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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Dec 17	The CA Lexicon available in the CAPLUS and CA files
NEWS 3	Feb 06	Engineering Information Encompass files have new names
NEWS 4	Feb 16	TOXLINE no longer being updated
NEWS 5	Apr 23	Search Derwent WPINDEX by chemical structure
NEWS 6	Apr 23	PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
NEWS 7	May 07	DGENE Reload
NEWS 8	Jun 20	Published patent applications (A1) are now in USPATFULL
NEWS 9	JUL 13	New SDI alert frequency now available in Derwent's DWPI and DPCI
NEWS 10	Aug 23	In-process records and more frequent updates now in MEDLINE
NEWS 11	Aug 23	PAGE IMAGES FOR 1947-1966 RECORDS IN CAPLUS AND CA
NEWS 12	Aug 23	Adis Newsletters (ADISNEWS) now available on STN
NEWS 13	Sep 17	IMSworld Pharmaceutical Company Directory name change to PHARMASEARCH
NEWS 14	Oct 09	Korean abstracts now included in Derwent World Patents Index
NEWS 15	Oct 09	Number of Derwent World Patents Index updates increased
NEWS 16	Oct 15	Calculated properties now in the REGISTRY/ZREGISTRY File
NEWS 17	Oct 22	Over 1 million reactions added to CASREACT
NEWS 18	Oct 22	DGENE GETSIM has been improved
NEWS 19	Oct 29	AAASD no longer available

NEWS EXPRESS	August 15 CURRENT WINDOWS VERSION IS V6.0c, CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP), AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
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FILE 'HOME' ENTERED AT 10:55:46 ON 13 NOV 2001

=> file embase biosis medline caplus uspatfull

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FULL ESTIMATED COST | 0.15 | 0.15

FILE 'EMBASE' ENTERED AT 10:56:04 ON 13 NOV 2001

FILE 'BIOSIS' ENTERED AT 10:56:04 ON 13 NOV 2001

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FILE 'CAPLUS' ENTERED AT 10:56:04 ON 13 NOV 2001

FILE 'USPATFULL' ENTERED AT 10:56:04 ON 13 NOV 2001


```
=> s alzheimer's
MISMATCHED QUOTE 'ALZHEIMER'S'
Quotation marks (or apostrophes) must be used in pairs,
one before and one after the expression you are setting
off or masking.

=> s alzheimer?
L1      135385 ALZHEIMER?

=> s dementia
L2      104566 DEMENTIA

=> s medium chain triglyceride? or MCT
L3       11150 MEDIUM CHAIN TRIGLYCERIDE? OR MCT

=> s l1 and l2 and l3
L4          11 L1 AND L2 AND L3

=> s l4 and py<2000
   2 FILES SEARCHED...
   4 FILES SEARCHED...
L5           5 L4 AND PY<2000

=> d l5 1-5 ab bib kwic

L5   ANSWER 1 OF 5  EMBASE  COPYRIGHT 2001 ELSEVIER SCI. B.V.
AB   Forty-two patients with organic dementia and 66 normal elderly
     subjects were investigated with the Meta-Contrast Technique (MCT
     ) elucidating emotional reactions and defensive strategies. Eleven
     patients with Alzheimer's disease (AD), 13 with frontotemporal
     degeneration (FTD), and 18 with multi-infarct dementia were
     studied. Defensive strategies were found to be related to the type of
     brain disorder and its localization. Patients with AD needed
significantly
     longer exposure times for recognition of the emotionally loaded picture
     configurations in the MCT and showed more often signs of
     anxiety. Signs of projection and depression were typical for patients
with
     FTD.
AN   90300982  EMBASE
```

DN 1990300982
TI Adaptation in different types of **dementia** and in normal elderly subjects.
AU Johanson A.; Gustafson L.; Smith G.J.W.; Risberg J.; Hagberg B.; Nilsson B.
CS Department of Psychogeriatrics, University of Lund; Lund, Sweden
SO Dementia, (1990) 1/2 (95-101).
ISSN: 1013-7424 CODEN: DEMNEU
CY Switzerland
DT Journal; Article
FS 008 Neurology and Neurosurgery
020 Gerontology and Geriatrics
LA English
SL English
TI Adaptation in different types of **dementia** and in normal elderly subjects.
SO Dementia, (1990) 1/2 (95-101).
ISSN: 1013-7424 CODEN: DEMNEU
AB Forty-two patients with organic **dementia** and 66 normal elderly subjects were investigated with the Meta-Contrast Technique (**MCT**) elucidating emotional reactions and defensive strategies. Eleven patients with **Alzheimer**'s disease (AD), 13 with frontotemporal degeneration (FTD), and 18 with multi-infarct **dementia** were studied. Defensive strategies were found to be related to the type of brain disorder and its localization. Patients with AD needed significantly longer exposure times for recognition of the emotionally loaded picture configurations in the **MCT** and showed more often signs of anxiety. Signs of projection and depression were typical for patients with FTD.
CT Medical Descriptors:
***alzheimer disease: ET, etiology**
*anxiety
*cognition
*defensive behavior
***dementia: ET, etiology**
***multiinfarct dementia: ET, etiology**
adult
aged
psychological aspect
controlled study
clinical article
human
male
female
article

L5 ANSWER 2 OF 5 USPATFULL
AB The present invention provides a number of screening methods for evaluatiing compounds capable of suppressing cytokine production either in vitro or in vivo. The methods generally involve stimulating the production of a cytokine in a cell, exposing a portion of the cells to a putative cytokine modulating agent and determining subsequent levels of cytokine production in the cells. Additionally, the present invention provides certain compounds identified by this method.
AN 1999:121379 USPATFULL
TI Screening methods for cytokine inhibitors
IN Mak, Vivian, Menlo Park, CA, United States

PA Adolor Corporation, Malvern, PA, United States (U.S. corporation)
PI US 5962477 19991005 <--
AI US 1998-97441 19980615 (9)
RLI Continuation-in-part of Ser. No. WO 1995-US4677, filed on 11 Apr 1995 which is a continuation-in-part of Ser. No. US 1995-400234, filed on 3 Mar 1995, now abandoned which is a continuation-in-part of Ser. No. US 1994-271287, filed on 6 Jul 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-225991, filed on 12 Apr 1994, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Tsang, Cecilia J.
LREP Seidman, Stephanie L.Heller Ehrman White & McAuliffe
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN 6 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 5138
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5962477 19991005 <--
DETD . . . diseases involving eosinophils (e.g. asthma, allergy, etc.), graft-versus-host reactions, bone resorption, inflammatory bowel disease, multiple sclerosis (MS), diabetes, AIDS and **Alzheimer** 's disease and/or the weight loss associated with **Alzheimer** patients.
DETD . . . in HIV-infected patients (see, Glass, et al., Neurology 43:2230-2237 (1993)). Levels of mRNA were significantly greater in patients with HIV-associated **dementia** than in AIDS patients without **dementia**, or in seronegative controls. Pentoxifylline (PTX), a drug which blocks TNF release, was tested in HIV-positive patients alone and together. . .
DETD . . . oil, petrolatum; mixes, such as primary esters of fractionated vegetable oil fatty acids with glycerine or propylene glycol, and interesterified **medium chain triglyceride** oils; fatty acids and fatty acid esters, such as amyl caproate, butyl acetate, caprylic acid, cetyl ester, diethyl sebacate, dioctyl. . .

L5 ANSWER 3 OF 5 USPATFULL
AB The present invention is related to a pharmaceutical formulation which is an oil-in-water emulsion for parenteral and oral use which comprises

(i) an emulsion-stabilizing surface active drug in high concentration;

(ii) optionally a pharmacologically inert oil;

(iii) optionally a surfactant;

(iv) water or a buffer; and

(v) an agent giving isotonicity to the final formulation;

the use of and a process for preparation of the formulation.
AN 1998:150483 USPATFULL
TI Emulsion formulation
IN Lundquist, Stefan, Stockholm, Sweden
PA Astra Aktiebolag, Sweden (non-U.S. corporation)
PI US 5843465 19981201 <--
WO 9509609 19950413 <--
AI US 1995-379486 19950130 (8)
WO 1994-SE926 19941005
19950130 PCT 371 date

. 19950130 PCT 102(e) date
PRAI SE 1993-3281 19931007
DT Utility
FS Granted
EXNAM Primary Examiner: MacMillan, Keith D.
LREP White & Case L.L.P.
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 597
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5843465 19981201 <--
WO 9509609 19950413 <--
SUMM . . . and/or spinal trauma; hypoxia and anoxia, such as from drowning, and including perinatal and neonatal hypoxic asphyxial brain damage; multi-infarct **dementia**; AIDS **dementia**; neurodegenerative diseases such as **Alzheimer**'s disease, Parkinson's disease, Huntington's chorea, epilepsy, multiple sclerosis and amytrophic lateral sclerosis; brain dysfunction in connection with surgery involving extracorporeal. . .
DETD . . . such as soybean oil, safflower oil, sesame oil, peanut oil, cottonseed oil, borago oil, sunflower oil, corn oil, olive oil, **medium chain triglycerides** (such as Miglyol.RTM.), or acetylated monoglycerides; c) a surfactant in an amount of from about 0.1 to 20 g per. . .
CLM What is claimed is:
. . . consisting of soybean oil, safflower oil, sesame oil, peanut oil, cottonseed oil, borago oil, sunflower oil, corn oil, olive oil, **medium chain triglycerides** and acetylated monoglycerides.

L5 ANSWER 4 OF 5 USPATFULL
AB The present invention is related to a pharmaceutical formulation which is an oil-in-water emulsion for parenteral and oral use which comprises

(i) an emulsion-stabilizing surface active drug in high concentration;

(ii) optionally a pharmacologically inert oil;

(iii) optionally a surfactant;

(iv) water or a buffer; and

(v) an agent giving isotonicity to the final formulation;

the use of and a process for preparation of the formulation.
AN 97:75826 USPATFULL
TI Preparing pharmaceutical formulation in form of oil-in-water emulsion
IN Lundquist, Stefan, Stockholm, Sweden
PA Astra Aktiebolag, Sodertalje, Sweden (non-U.S. corporation)
PI US 5660837 19970826 <--
AI US 1995-460046 19950602 (8)
RLI Division of Ser. No. US 1995-379486, filed on 30 Jan 1995
PRAI SE 1993-3281 19931007
DT Utility
FS Granted
EXNAM Primary Examiner: Lovering, Richard D.
LREP White & Case
CLMN Number of Claims: 2

ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 582
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5660837 19970826 <--
SUMM . . . and/or spinal trauma; hypoxia and anoxia, such as from drowning, and including perinatal and neonatal hypoxic asphyxial brain damage; multi-infarct **dementia**; AIDS **dementia**; neurodegenerative diseases such as **Alzheimer**'s disease, Parkinson's disease, Huntington's chorea, epilepsy, multiple sclerosis and amytrophic lateral sclerosis; brain dysfunction in connection with surgery involving extracorporeal. . .
DETD . . . such as soybean oil, safflower oil, sesame oil, peanut oil, cottonseed oil, borago oil, sunflower oil, corn oil, olive oil, **medium chain triglycerides** (such as Miglyol.RTM.), or acetylated monoglycerides; c) a surfactant in an amount of from about 0.1 to 20 g per. . .

L5 ANSWER 5 OF 5 USPATFULL
AB The present invention relates to compounds of the formula: ##STR1## wherein R is H or alkyl;

Y.sup.1 is --CH.dbd. or --N.dbd.; and

Y.sup.2 --CH.dbd., --C(OH).dbd., --C(NO.sub.2).dbd., --C(NH.sub.2).dbd., --C(Hal).dbd., --N.dbd.;

X is cycloalkenyl; bicyclo[2.2.1]hept-2-yl, optionally substituted by phenyl-2-oxo-5 -methoxymethyl-oxazolidinyl; bicyclo[2.2.1]-hept-5 -en-2-yl; adamantyl; or cycloalkyl or piperidinyl, optionally substituted by amino, alkyl, --CN, oxo hydroxyimino, ethylenedioxy

or by --OR.sup.1,

R.sup.1 is --CH(C.sub.6 H.sub.5).sub.2, --(CH.sub.2).sub.n C.sub.6 H.sub.5, alkyl, H, --(CH.sub.2).sub.n NHCOCH.sub.3, --(CH.sub.2).sub.n NH.sub.2, --(CH.sub.2).sub.n CN, --(CH.sub.2).sub.n SCH.sub.3 --(CH.sub.2).sub.n SO.sub.2 CH.sub.3, --CO-lower-alkyl, --COC.sub.6 H.sub.5, optionally substituted by oxazolidine;

or by .dbd.CR.sup.2 R.sup.3,

R.sup.2 is alkyl

R.sup.3 is H, --CN, alkyl, phenyl or COO-alkyl;

or by --(CH.sub.2).sub.n R.sup.4

R.sup.4 is --CN, amino, --NHCOCH.sub.3, --COC.sub.6 H.sub.5 Hal, phenyl or hydroxy;

or by --COR.sup.5,

R.sup.5 is alkyl, --CH.dbd.CH--C.sub.6 H.sub.5, --C.sub.6 H.sub.5, --C.sub.6 H.sub.5 CF.sub.3 or --O-alkyl;

or by --NR.sup.6 R.sup.7,

R.sup.6 is or --COCH.sub.3 ;

R.sup.7 is --COCH.sub.3, benzyl or --(CH.sub.2).sub.n NHCOC.sub.6 H.sub.4 Hal; and

n is 1-3;

These can be used for the prevention or control of depressive, panic and anxiety states, and treatment of certain cognitive disorders and neurodegenerative diseases.

AN 96:104018 USPATFULL
TI Oxazolidinone derivatives
IN Borgulya, Janos, Basel, Switzerland
Bruderer, Hans, Biel-Benken, Switzerland
Jakob-Roetne, Roland, Inzlingen, Germany, Federal Republic of
R over, Stephan, Inzlingen, Germany, Federal Republic of
PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 5574055 19961112 <--
AI US 1994-349119 19941202 (8)
PRAI CH 1993-3701 19931213
CH 1994-2927 19940927
DT Utility
FS Granted
EXNAM Primary Examiner: Daus, Donald G.
LREP Johnston, George W., Silverman, Robert A.
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2400
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5574055 19961112 <--

SUMM . . . for the treatment of depressive states, panic and anxiety states, cognitive disorders and neurodegenerative diseases such as Parkinson's disease and **Alzheimer**'s disease.

SUMM . . . control or prevention of depressive states, panic and anxiety states, cognitive disorders and neurodegenerative diseases such as Parkinson's disease and **Alzheimer**'s disease and the use of compounds of formula I and salts defined earlier for the production of medicaments for the. . . control or prevention of depressive states, panic and anxiety states, cognitive disorders and neurodegenerative diseases such as Parkinson's disease and **Alzheimer**'s disease.

SUMM . . . anxiety states, cognitive disorders and neurodegenerative diseases. Examples of such diseases are parkinsonic age-related memory impairment, primary and secondary degenerative **dementia**, for example **dementia** of the **Alzheimer** type or multi-infarct caused **dementia** and cerebrovascular disorders and consequences of cerebral damage.

SUMM . . . be used in the control or prevention of depressive states, cognitive disorders and neurodegenerative diseases such as Parkinson's disease and **Alzheimer**'s disease. The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each. . .

DETD

Active ingredient	100 mg
Medium chain triglyceride	300 mg
	400 mg

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 NEWS 19  Oct 29  AAASD no longer available

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               CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP),
               AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
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=> file medline caplus uspatfull napralert
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                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.15       0.15

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University of Illinois at Chicago.

=> s medium chain triglyceride? or MCT or babassu oil or coconut oil or
cohune oil or palm kernel oil or tucum oil
L1       32264 MEDIUM CHAIN TRIGLYCERIDE? OR MCT OR BABASSU OIL OR COCONUT
OIL
                OR COHUNE OIL OR PALM KERNEL OIL OR TUCUM OIL

=> s dementia
L2       50462 DEMENTIA

=> s l1 and l2
L3         470 L1 AND L2

=> s l3 and alzheimer
L4         383 L3 AND ALZHEIMER

=> s l4 and py<2000
L5         285 L4 AND PY<2000

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6          285 DUP REM L5 (0 DUPLICATES REMOVED)

=> s emulsi?
L7      403099 EMULSI?

=> s l6 and l7
L8         252 L6 AND L7

=> s oral or intavenous
L9      485168 ORAL OR INTAVENOUS

=> s l8 and l9
L10        251 L8 AND L9

=> s oral or intravenous
L11     700327 ORAL OR INTRAVENOUS

=> s l8 and l11
L12        251 L8 AND L11

=> s neuron?
L13     425406 NEURON?
```

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=> s l12 and l3
L14         251 L12 AND L3

=> s l12 and l13
L15         145 L12 AND L13

=> s medium chain triglyceride? or MCT
L16        6989 MEDIUM CHAIN TRIGLYCERIDE? OR MCT

=> s l15 adn l16
MISSING OPERATOR L15 ADN
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l15 and l16
L17           3 L15 AND L16

=> d l17

L17  ANSWER 1 OF 3  USPATFULL
AN     1999:121379  USPATFULL
TI     Screening methods for cytokine inhibitors
IN     Mak, Vivian, Menlo Park, CA, United States
PA     Adolor Corporation, Malvern, PA, United States (U.S. corporation)
PI     US 5962477              19991005                              <--
AI     US 1998-97441           19980615 (9)
RLI    Continuation-in-part of Ser. No. WO 1995-US4677, filed on 11 Apr 1995
       which is a continuation-in-part of Ser. No. US 1995-400234, filed on 3
       Mar 1995, now abandoned which is a continuation-in-part of Ser. No. US
       1994-271287, filed on 6 Jul 1994, now abandoned which is a
       continuation-in-part of Ser. No. US 1994-225991, filed on 12 Apr 1994,
       now abandoned
DT     Utility
FS     Granted
LN.CNT 5138
INCL   INCLM: 514/327.000
       INCLS: 424/078.050
NCL    NCLM:  514/327.000
       NCLS:  424/078.050
IC     [6]
       ICM: A61K031-445
EXF    514/327; 424/78.05
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> d kwic

L17  ANSWER 1 OF 3  USPATFULL
PI     US 5962477              19991005                              <--
DETD   (2) Oral Formulations
DETD   . . . diseases involving eosinophils (e.g. asthma, allergy, etc.),
       graft-versus-host reactions, bone resorption, inflammatory bowel
       disease, multiple sclerosis (MS), diabetes, AIDS and Alzheimer
       's disease and/or the weight loss associated with Alzheimer
       patients.
DETD   . . . in HIV-infected patients (see, Glass, et al., Neurology
       43:2230-2237 (1993)). Levels of mRNA were significantly greater in
       patients with HIV-associated dementia than in AIDS patients
       without dementia, or in seronegative controls. Pentoxifylline
```

(PTX), a drug which blocks TNF release, was tested in HIV-positive patients alone and together. . .

DETD . . . and the probe is visualized. For example, where the label is .sup.35 S, the slides are covered with a photographic **emulsion** and developed after a week-long exposure. For DIG-labeled probes, a color development procedure is performed that is similar to that. . .

DETD . . . G. D. Searle and Company, and under the trade name ISOPTIN.RTM. from Knoll Pharmaceutical Company. Verapamil is available in an **oral** dosage form, an **oral** form with sustained release, and an injectable form which is typically used intravenously. If desired, the practitioner may use one. . .

DETD . . . modulating inflammation are applied to the skin, either iontophoretically, sonophoretically, topically, or through other routes of drug administration, such as **oral** (PO), intraperitoneal (IP), **intravenous** (IV), vaginal, rectal, intramuscular (IM), aerosol, nasal spray, ocular, transdermal, colonic, and the like.

DETD . . . PHARMACEUTICAL SCIENCES, the full disclosures of which are incorporated herein by reference. Methods for administration are discussed therein, e.g., for **oral**, **intravenous**, intraperitoneal, or intramuscular administration, and others. Pharmaceutically acceptable carriers will include water, saline, buffers, and other compounds described, e.g., in. . .

DETD . . . with an aqueous or oily base and will, in general, also include one or more of the following: stabilizing agents, **emulsifying** agents, dispersing agents, suspending agents, thickening agents, coloring agents, perfumes, and the like.

DETD (2) **Oral** Formulations

DETD For delivery to the buccal membranes, typically an **oral** formulation, such as a lozenge, tablet, or capsule will be used. The method of manufacture of these formulations are known. . . either a pharmacological agent or a substance containing the agent (as described in U.S. Pat. No. 4,806,356); and encapsulation. Another **oral** formulation is one that can be applied with an adhesive, such as the cellulose derivative, hydroxypropyl cellulose, to the **oral** mucosa, for example as described in U.S. Pat. No. 4,940,587. This buccal adhesive formulation, when applied to the buccal mucosa,. . .

DETD Colon-targeted delivery can be carried out using an **oral** dosage form such as that described in U.S. Pat. No. 4,111,201. These osmotic pump delivery systems for **oral** formulations (termed OROS.TM.) will be particularly useful for the treatment of systemic inflammatory bowel disease. Other **oral** delivery systems which tend to localize or concentrate the administered drug in the colon would be quite useful for treating. . .

DETD . . . erosion), insoluble inserts (e.g., medicated contact lenses such as Ocusert.RTM., etc.), gels (e.g., Gelrite.RTM.), liposomal and drug delivery via nanoparticles (**emulsion**, suspension, etc.), and ointment (See Edman, BIOPHARMACEUTICS OF OCULAR DRUG DELIVERY, CRC Press, 1993).

DETD . . . the lipid milieu of the stratum corneum at a lower current density. Thus, the epidermis, as well as the peripheral **neurons** surrounding the hair follicles and sweat ducts, will be able to experience the electrical stimulation.

DETD . . . such as azacycloalkanes; essential oils, such as almond oil, amyl butyrate, apricot kernel oil, avocado oil, camphor, castor oil, 1-carvone, **coconut oil**, corn oil, cotton seed oil, eugenol, menthol, oil of anise, oil of clove, orange oil, peanut oil,

peppermint oil, rose. . . oil, petrolatum; mixes, such as primary esters of fractionated vegetable oil fatty acids with glycerine or propylene glycol, and interesterified **medium chain triglyceride** oils; fatty acids and fatty acid esters, such as amyl caproate, butyl acetate, caprylic acid, cetyl ester, diethyl sebacate, dioctyl. . .

DETD For delivery to the buccal membranes, typically an **oral** formulation, such as a lozenge, tablet, or capsule will be used. The method of manufacture of these formulations are known. . . either a pharmacological agent or a substance containing the agent (as described in U.S. Pat. No. 4,806,356); and encapsulation. Another **oral** formulation is one that can be applied with an adhesive, such as the cellulose derivative, hydroxypropyl cellulose, to the **oral** mucosa, for example as described in U.S. Pat. No. 4,940,587. This buccal adhesive formulation, when applied to the buccal mucosa,. . .

DETD . . . erosion), insoluble inserts (e.g., medicated contact lenses such as Ocusert.RTM., etc.), gels (e.g., Gelrite.RTM.), liposomal and drug delivery via nanoparticles (**emulsion**, suspension, etc.), and ointment (See Edman, BIOPHARMACEUTICS OF OCULAR DRUG DELIVERY, CRC Press, 1993).

DETD . . . to the target tissue. Further, it is known in the art that the fraction of drug absorbed is 10-100% via **oral** administration, 100% intravenously, and about 2-100% via topical delivery. Thus, the total amount of drug which is administered to achieve. . .

DETD An initial **oral** dose of about 10 to about 180 mg per day of (+)-verapamil is recommended. The dosage may be increased, usually. . .

DETD . . . least 2 minutes. This dosage may be repeated in about 30 minutes after the initial dose. For pediatric patients, the **intravenous** dosage is about 0.01 to about 0.2 mg per kg body weight, usually given in a single dose of about. . . mg per kg body weight is typically given. Usually, it is not advisable to exceed 10 mg as a single **intravenous** dose.

DETD After **oral** administration, verapamil is well absorbed and is rapidly bio-transformed during its first pass through the portal circulation. Subsequent bioavailability ranges from about 20% to about 35%. After about between one and two after **oral** administration, peak plasma concentrations are reached. The mean elimination half-life in single-dose studies ranges from about 2.8 to about 7.4. . .

DETD . . . in the neural polarity of the C-fibers, typically resulting from electrotransport, the release of neuropeptides and/or neurotransmitters from the afferent **neurons** and hence, the release of proinflammatory mediators can be prevented.

DETD . . . typically undress and undergo a complete examination as some signs may not be visible to the patient on self-examination. The **oral** mucosa, anogenital area, scalp, and nails are especially relevant areas of examination. A biopsy of the may be required for. . .

DETD . . . Screening tests as in Example 3 are performed. At the practitioner's discretion, the patient's current medications can be continued, and **oral** (+)-verapamil is added to the current regimen. The (+)-verapamil is started at 20 mg twice a day. If tolerated, the. . .

=> d B
'B' IS NOT A VALID FORMAT FOR FILE 'USPATFULL'

The following are valid formats:

The default display format is STD.

```
ABS -------- AB
ALL -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PTERM, DCD,
             RLI, PRAI, DT, FS, REP, REN, EXNAM, LREP, CLMN, ECL,
             DRWN, AB, GOVI, PARN, SUMM, DRWD, DETD, CLM, INCL,
             INCLM, INCLS, NCL, NCLM, NCLS, IC, ICM, ICS, EXF,
             ARTU
ALLG ------- ALL plus PAGE.DRAW
BIB -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PTERM, DCD, RLI,
             PRAI, DT, FS, EXNAM, LREP, CLMN, ECL, DRWN, LN.CNT
CAS -------- OS, CC, SX, ST, IT
CBIB ------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PRAI, DT, FS
DALL ------- ALL, delimited for post-processing
FPALL ------ PI, TI, IN, INA, PA, PAA, PAT, PETRM, DCD, AI,
             RLI, PRAI, IC, ICM, ICS, INCL, INCLM, INCLS, NCL, NCLM,
             NCLS, EXF, REP, REN,ARTU, EXNAM, LREP, CLMN, DRWN, AB,
             PARN, SUMM, DRWD, DETD, CLM
FPBIB ------ PI, TI, IN, INA, PA, PAA, PAT, PTERM, DCD, AI,
             RLI, PRAI, REP, REN, EXNAM, LREP, CLM, CLMN, DRWN
FHITSTR ---- HIT RN, its text modification, its CA index name, and
             its structure diagram
FPG -------- FP plus PAGE.DRAW
GI --------- PN and page image numbers
HIT -------- All fields containing hit terms
HITRN ------ HIT RN and its text modification
HITSTR ----- HIT RN, its text modification, its CA index name, and
             its structure diagram
IABS ------- ABS, indented with text labels
IALL ------- ALL, indented with text labels
IALLG ------ IALL plus PAGE.DRAW
IND -------- INCL, INCLM, INCLS, NCL, NCLM, NCLS, IC, ICM, ICS,
             EXF, ARTU, OS, CC, SX, ST, IT
ISTD ------- STD, indented with text labels
KWIC ------- All hit terms plus 20 words on either side
MAX -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PTERM, DCD,
             RLI, PRAI, DT, FS, REP, REN, EXNAM, LREP, CLMN, ECL,
             DRWN, AB, GOVI, PARN, SUMM, DRWD, DETD, CLM, INCL,
             INCLM, INCLS, NCL, NCLM, NCLS, IC, ICM, ICS, EXF,
             ARTU OS, CC, SX, ST, IT
SBIB ------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, RLI, PRAI,
             DT, FS, LN.CNT
SCAN ------- AN, TI, NCL, NCLM, NCLS, IC, ICM, ICS (random display
             without answer number.  SCAN must be entered on the
             same line as DISPLAY, e.g., D SCAN)
STD -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, RLI, PRAI,
             DT, FS, LN.CNT, INCL, INCLM, INCLS, NCL, NCLM, NCLS,
             IC, ICM, ICS, EXF (STD is the default)
TRIAL ------ AN, TI, INCL, INCLM, INCLS, NCL, NCLM, NCLS, IC,
             ICM, ICS
```

The DISPLAY BROWSE command allows the user to move forward and backward within a document, and search for a particular character string within a document display. To do this, enter one of the following at the colon prompt (:).

```
F ---------- move forward to the next field or paragraph
Fn --------- move forward n fields or paragraphs
```

B ---------- move backward to the next field or paragraph
Bn ---------- move backward n fields or paragraphs
SEA term ---- search for the next instance of term
SEA- term --- search backwards for the last instance of term

BIBG ------- BIB plus PAGE.DRAW
FP --------- PI, TI, IN, INA, PA, PAA, PAT, PTERM, DCD, AI, RLI,
PRAI, IC, ICM, ICS, INCL, INCLM, INCLS, NCL,
NCLM, NCLS, EXF, REP, REN, ARTU, EXNAM, LREP,
CLMN, DRWN, AB
IBIB ------- BIB, indented with text labels
IBIBG ------ IBIB plus PAGE.DRAW
IMAX ------- MAX, indented with text labels
OCC -------- List of display fields containing hit terms
and number of occurrences in each field
The order of the fields for F and B is the same as the order in
the ALL format. If term is not specified when using the SEA
option, the term entered in the previous search request is used.
Note that SEA makes no distinction between upper and lower case
letters.
ENTER DISPLAY FORMAT (STD):AB

L17 ANSWER 1 OF 3 USPATFULL
AB The present invention provides a number of screening methods for
evaluatiing compounds capable of suppressing cytokine production either
in vitro or in vivo. The methods generally involve stimulating the
production of a cytokine in a cell, exposing a portion of the cells to
a
putative cytokine modulating agent and determining subsequent levels of
cytokine production in the cells. Additionally, the present invention
provides certain compounds identified by this method.

=> D 2-3 AB BIB KWIC

L17 ANSWER 2 OF 3 USPATFULL
AB The present invention is related to a pharmaceutical formulation which
is an oil-in-water **emulsion** for parenteral and **oral**
use which comprises

(i) an **emulsion**-stabilizing surface active drug in high
concentration;

(ii) optionally a pharmacologically inert oil;

(iii) optionally a surfactant;

(iv) water or a buffer; and

(v) an agent giving isotonicity to the final formulation;

the use of and a process for preparation of the formulation.
AN 1998:150483 USPATFULL
TI **Emulsion** formulation
IN Lundquist, Stefan, Stockholm, Sweden
PA Astra Aktiebolag, Sweden (non-U.S. corporation)
PI US 5843465 19981201 <--
WO 9509609 19950413
AI US 1995-379486 19950130 (8)
WO 1994-SE926 19941005

19950130 PCT 371 date
19950130 PCT 102(e) date
PRAI SE 1993-3281 19931007
DT Utility
FS Granted
EXNAM Primary Examiner: MacMillan, Keith D.
LREP White & Case L.L.P.
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 597
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI **Emulsion** formulation
PI US 5843465 19981201 <--
WO 9509609 19950413
AB The present invention is related to a pharmaceutical formulation which is an oil-in-water **emulsion** for parenteral and **oral** use which comprises
AB (i) an **emulsion**-stabilizing surface active drug in high concentration;
SUMM This invention relates to a novel pharmaceutical formulation comprising an **emulsion**-stabilizing surface active drug which may be administered parenterally or orally; and to the use of and a process for preparing. . .
SUMM . . . the CMZ-edisilate at room temperature (the product must be stored at +4.degree.-8.degree. C.) and the substantial sorption of CMZ by **intravenous** infusion giving sets. This sorption to plastics results in a safety problem in the clinic, especially when treating disorders requiring very accurate dosing. Finally, the **oral** liquid dosage form, a 5 w/v % syrup of CMZ-edisilate, also has a number of disadvantages such as poor stability. . .
SUMM . . . object of the invention is to provide a novel, clinically and pharmaceutically acceptable and useful formulation which is an oil-in-water **emulsion** for parenteral and **oral** use which comprises
SUMM (i) an **emulsion**-stabilizing surface active drug in high concentration;
SUMM The present invention is preferably related to **emulsion**-stabilizing surface active drugs having an anti-convulsant or sedative-hypnotic effect or drugs for preventing and/or treating neurodegeneration caused by acute and chronic neuropsychiatric disorders characterised by progressive processes that sooner or later lead to **neuronal** cell death and dysfunction. Such disorders include stroke; cerebral ischaemia; dysfunctions resulting from brain and/or spinal trauma; hypoxia and anoxia, such as from drowning, and including perinatal and neonatal hypoxic asphyxial brain damage; multi-infarct **dementia**; AIDS **dementia**; neurodegenerative diseases such as **Alzheimer**'s disease, Parkinson's disease, Huntington's chorea, epilepsy, multiple sclerosis and amytrophic lateral sclerosis; brain dysfunction in connection with surgery involving extracorporeal. . . to neurotoxins or radiation. This utility is manifested, for example, by the ability of the claimed formulation to inhibit delayed **neuronal** death in the gerbil bilateral occlusion model of ischaemia.
SUMM Preferred **emulsion**-stabilizing surface active drugs are the CMZ-base which is an oil at room temperature, and/or some analogues thereof which are oils. . . besides having a pharmacological effect, as a stabilizing surfactant or co-surfactant at the large interface in

an oil in water **emulsion** system or in another aspect of the invention, functioning as the actual oil phase in an **emulsion** system.

SUMM . . . to the above mentioned drugs but could also be used to include any other drug which displays suitable amphiphilic and **emulsion**-stabilizing properties.

SUMM A conventional pharmacologically inert oil is included as a component in the formulation when the **emulsion**-stabilizing drug is not itself used as the internal oil phase.

SUMM . . . surfactant is included as a component in the formulation when the drug functions as the internal oil phase of the **emulsion**.

SUMM By means of the present invention the undesirable properties of both the parenteral and the **oral** dosage form, mentioned in the background of the invention, can be avoided. Certain compounds, because of their chemical structure, have. . . fundamental changes in the nature of the interface which are of considerable importance in different contexts. For example, in an **emulsion** the adsorption of a surfactant at the oil-water interface lowers the interfacial tension thereby aiding in the dispersal of the. . . allow storage for a long period of time (typically two years) of pharmaceutically interesting two-phase systems such as for example **emulsions**. The geometrical shape of the amphiphilic molecule and the presence of any substituents in said molecule can have an appreciable effect on its stabilizing properties. Surprisingly, it has been found that e.g. CMZ and said analogues display excellent **emulsion**-stabilizing properties which allow **emulsions** of these compounds to be stored for a long period of time. Due to the geometrical shape and the amphiphilic properties of the drug molecule it is adsorbed at the surface of the droplets in the **emulsion**, forming a rigid and tightly packed interfacial film thereby reducing the possibility of collisions leading to droplet coalescence and consequently. . .

SUMM . . . number of other drugs with hydrophobic portions comprising aromatic and/or heterocyclic ring systems or a steroid skeleton also display good **emulsion**-stabilizing properties.

SUMM Examples of the types of drugs, besides CMZ and its analogues, which have been found beneficial to use as **emulsion**-stabilizing agents include: antidepressants, neuroleptics, immunosuppressants, immunomodulators, antibiotics, antiinflammatory agents, proton pump inhibitors, calcium channel blockers, such as felodipine, and beta. . .

SUMM . . . usually observed that mixtures of conventional surfactants form even more stable systems than do single surfactants, even with very dilute **emulsions**, it has in some cases been found beneficial to use **emulsion**-stabilizing surface active drugs as co-surfactants together with any conventional pharmaceutically acceptable non-ionic surfactants, such as the poloxamers F68, F127 or. . . used by a person skilled in the art it is possible to manufacture a stable two-phase system like e.g. an **emulsion** of any appropriate drug mentioned above, where the stabilizing effect is due to the surface active drug alone or the. . . any other appropriate drug which is in the liquid state, could also function as the actual oil phase in an **emulsion** system in that way making it possible to incorporate a high concentration of the drug. In the latter case said. . .

DRWD FIG. 1A shows the .sup.13 C-NMR spectra of an **emulsion** with

CMZ;

DRWD FIG. 1B shows the .sup.13 C-NMR spectra of an **emulsion** without CMZ;

DRWD . . . the chemical shifts of the carbonyl carbons of a phospholipid, located at the interface between oil and water in the **emulsion** system, in the presence of CMZ; and

DETD . . . formulation in the former case can be established by known techniques such as .sup.13 C-NMR and a spectra of an **emulsion** with and without CMZ is shown in FIG. 1. Using .sup.13 C-NMR chemical shift determinations, it is possible to obtain information on the location of the CMZ-molecule in the **emulsion** system. For example, according to FIG. 2 the chemical shifts of the carbonyl carbons of a phospholipid, which are located at the interface in the **emulsion** system, is changed in the presence of CMZ. In fact, there is a linear relationship between the concentration of CMZ. . . of the carbonyl carbons (FIG. 2). The chemical shifts of the methylene carbons, being located in the core of the **emulsion** droplets is essentially unaffected by the presence of CMZ which can also be seen in FIG. 2. Notably, the effects. . . immediate environment (.ltoreq.5 .ANG.), these findings clearly show that CMZ is primarily located in the surface region of the **emulsion** droplets.

DETD Surprisingly, it has been found that the presence of **emulsion** -stabilizing surface active drugs at the interface of an **emulsion** not only produces **emulsions** with excellent physical stability but also makes it possible to improve poor chemical stability of the drug in some cases,. . . any other appropriate drug which is in the liquid state has been used as the actual oil phase of an **emulsion**, thus allowing for a prolonged storage at room temperature. It has also become possible to substantially increase the drug concentration. . . Hence, the safety of e.g. CMZ in the clinic was improved by a substantially reduced sorption of the drug by **intravenous** infusion giving sets and moreover by giving the **emulsion** orally it was found that this type of formulation was also capable of improving the conventional liquid **oral** dosage form by a considerably better masking of the bitter taste of CMZ and at the same time solving the. . .

DETD in the case where the **emulsion**-stabilizing surface active drug is not itself used as the internal oil phase by

DETD adding the **emulsion**-stabilizing surface active drug and an optional conventional surfactant to a two-phase, oil-water-system at room temperature;

DETD allowing the **emulsion**-stabilizing surface active drug or the **emulsion**-stabilizing surface active drug together with the conventional surfactant to equilibrate at the interface;

DETD homogenizing by high pressure technique whereby a stable **emulsion** is obtained which has a droplet size distribution where the main fraction is below 200 nm;

DETD dispersing the **emulsion**-stabilizing surface active drug together with a conventional surfactant in water at room temperature;

DETD homogenizing by high pressure technique; whereby a stable **emulsion** is obtained which has a droplet size distribution where the main fraction is below 200 nm.

DETD This novel formulation comprises in general the **emulsion** -stabilizing surface active drug in a concentration from about 0.01 to 5% w/v.

DETD More particularly, the novel formulation of the invention comprises: a) the **emulsion**-stabilizing surface active drug in an amount of

from about 0.01 to 5.0 g per 100 ml of the final formulation;. . . such as soybean oil, safflower oil, sesame oil, peanut oil, cottonseed oil, borago oil, sunflower oil, corn oil, olive oil, **medium chain triglycerides** (such as Miglyol.RTM.), or acetylated monoglycerides; c) a surfactant in an amount of from about 0.1 to 20 g per. . .

DETD The administration in the novel method of treatment of this invention may conveniently be **oral** or parenteral at a dosage level of, for example, about 1 to 3000 mg/kg, preferably about 10 to 1000 mg/kg. . . 1 to 4 doses or treatments per day. The dose will depend on the route of administration preferred routes being **oral** or **intravenous** administration. It will be appreciated that the severity of the disease, the age of the patient and other factors normally. . .

DETD Oil-in-water **emulsions** of CMZ for **intravenous** and **oral** use were prepared from the following components:

DETD In a first step the **emulsion**-stabilizing drug and a surfactant were added to a two-phase system, oil-water, at room temperature and were subsequently allowed to equilibrate at the interface. This formulation, together with additional indicated components in the formula, was homogenized and the resulting **emulsion** was stable and had an average droplet size below 100 nm and could easily be sterile filtered (200 nm filter).

DETD Oil-in-water **emulsions** were prepared as described in Examples 1-2 with the following components:

DETD Oil-in-water **emulsions** were prepared as described in Examples 1-2 with the following components:

DETD Oil-in-water **emulsions**, according to Examples 9-12, were prepared with the only difference that a sodium carbonate buffer pH 7.0 was used to. . .

DETD Oil-in-water **emulsions** were prepared as described in Examples 1-2 with the following components:

DETD Oil-in-water **emulsions** were prepared according to Examples 17-20 with the only difference that a sodium carbonate buffer pH 7.0 was used to. . .

DETD Oil in water **emulsions**, where the **emulsion**-stabilizing drug was used as the sole stabilizing agent in the system, were prepared from the following components:

DETD In a first step the **emulsion**-stabilizing drug was added to a two-phase system, oil-water, at room temperature and was subsequently allowed to equilibrate at the interface. This formulation, together with additional indicated components in the formula, was homogenized and the resulting **emulsion** was stable and had an average droplet size below 100 nm and could easily be sterile filtered (200 nm filter).

DETD Oil in water **emulsions** were prepared as described in Examples 25-26 with the following components:

DETD **Emulsions** where the drug functions as the internal oil-phase of the system were prepared from the following components:

DETD In a first step the drug was dispersed in water at room temperature. An **emulsion** was then prepared from the resulting drug-water dispersion, together with additional indicated components in the formula. The resulting **emulsion** was stable and had an average droplet size below 100 nm and could easily be sterile filtered (200 nm filter).

DETD **Emulsions** according to Examples 31-32 were prepared with the following components:

DETD **Emulsions** according to Examples 31-32 were prepared with the

following components:

DETD **Emulsions** according to Examples 39-42 were prepared with the only difference that a sodium carbonate buffer pH 7.0 was used to. . .

CLM What is claimed is:

1. A sterile pharmaceutical formulation of an oil-in-water **emulsion** for parenteral and **oral** administration which comprises: (i) an **emulsion**-stabilizing surface active drug in a concentration ranging from 0.01 g to 5.0 g per 100 ml of the final formulation;. . . an internal oil; (iv) water or a buffer; and (v) an

agent giving isotonicity to the final formulation; the formulated **emulsion** having a major fraction of stable droplets having a size below 200 nm so as to be suitable for sterile. . .

2. The formulation according to claim 1 wherein the **emulsion** -stabilizing surface active drug is a drug for preventing neurodegeneration, treating neurodegeneration, or having an anti-convulsant or sedative-hypnotic effect.

3. The formulation according to claim 1 wherein the **emulsion** -stabilizing surface active drug is selected from the group consisting of 5-(2-chloroethyl)-4-methylthiazole, 5-(2-chloroethyl)-4-methyloxazole, 5-(2-chloroethyl)-2,4-dimethyloxazole, 5-(2-chloroethyl)-2,4-dimethylthiazole, 5-(2-chloro-1-hydroxyethyl)-4-methylthiazole and its optical isomers.

4. The formulation according to claim 3 wherein the **emulsion** -stabilizing surface active drug is 5-(2-chloroethyl)-4-methylthiazole.

. . . consisting of soybean oil, safflower oil, sesame oil, peanut oil, cottonseed oil, borago oil, sunflower oil, corn oil, olive oil, **medium chain triglycerides** and acetylated monoglycerides.

14. A sterile pharmaceutical **emulsion** preparation for parenteral or **oral** administration comprising an **emulsion**-stabilizing surface active drug in base form which is dispersed and equilibrated in a two-phase, oil-water-system which further comprises a pharmacologically. . . a sufficient amount of an agent for isotonicity; the preparation being homogenized under high pressure so as to obtain an **emulsion** which has a droplet size distribution where the main fraction is below 200 nm; and sterile filtered through a 0.2. . .

L17 ANSWER 3 OF 3 USPATFULL

AB The present invention is related to a pharmaceutical formulation which is an oil-in-water **emulsion** for parenteral and **oral** use which comprises

(i) an **emulsion**-stabilizing surface active drug in high concentration;

(ii) optionally a pharmacologically inert oil;

(iii) optionally a surfactant;

(iv) water or a buffer; and

(v) an agent giving isotonicity to the final formulation;

the use of and a process for preparation of the formulation.
AN 97:75826 USPATFULL
TI Preparing pharmaceutical formulation in form of oil-in-water **emulsion**
IN Lundquist, Stefan, Stockholm, Sweden
PA Astra Aktiebolag, Sodertalje, Sweden (non-U.S. corporation)
PI US 5660837 19970826 <--
AI US 1995-460046 19950602 (8)
RLI Division of Ser. No. US 1995-379486, filed on 30 Jan 1995
PRAI SE 1993-3281 19931007
DT Utility
FS Granted
EXNAM Primary Examiner: Lovering, Richard D.
LREP White & Case
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 582
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Preparing pharmaceutical formulation in form of oil-in-water **emulsion**
PI US 5660837 19970826 <--
AB The present invention is related to a pharmaceutical formulation which is an oil-in-water **emulsion** for parenteral and **oral** use which comprises
AB (i) an **emulsion**-stabilizing surface active drug in high concentration;
SUMM This invention relates to a novel pharmaceutical formulation comprising an **emulsion**-stabilizing surface active drug which may be administered parenterally or orally; and to the use of and a process for preparing. . .
SUMM . . . the CMZ-edisilate at room temperature (the product must be stored at +4.degree.-8.degree. C.) and the substantial sorption of CMZ by **intravenous** infusion giving sets. This sorption to plastics results in a safety problem in the clinic, especially when treating disorders requiring very accurate dosing. Finally, the **oral** liquid dosage form, a 5 w/v % syrup of CMZ-edisilate, also has a number of disadvantages such as poor stability. . .
SUMM . . . object of the invention is to provide a novel, clinically and pharmaceutically acceptable and useful formulation which is an oil-in-water **emulsion** for parenteral and **oral** use which comprises
SUMM (i) an **emulsion**-stabilizing surface active drug in high concentration;
SUMM The present invention is preferably related to **emulsion** -stabilizing surface active drugs having an anti-convulsant or sedative-hypnotic effect or drugs for preventing and/or treating neurodegeneration caused by acute and chronic neuropsychiatric disorders characterised by progressive processes that sooner or later lead to **neuronal** cell death and dysfunction. Such disorders include stroke; cerebral ischaemia; dysfunctions resulting from brain and/or spinal trauma; hypoxia and anoxia, such as from drowning, and including perinatal and neonatal hypoxic asphyxial brain damage; multi-infarct **dementia**; AIDS **dementia**; neurodegenerative diseases such as **Alzheimer**'s disease, Parkinson's disease, Huntington's chorea, epilepsy, multiple sclerosis and amytrophic lateral sclerosis; brain dysfunction in connection with surgery involving extracorporeal. . . to neurotoxins or radiation. This utility is manifested, for

example, by the ability of the claimed formulation to inhibit delayed **neuronal** death in the gerbil bilateral occlusion model of ischaemia.

SUMM Preferred **emulsion**-stabilizing surface active drugs are the CMZ-base which is an oil at room temperature, and/or some analogues thereof which are oils. . . besides having a pharmacological effect, as a stabilizing surfactant or co-surfactant at the large interface in an oil in water **emulsion** system or in another aspect of the invention, functioning as the actual oil phase in an **emulsion** system.

SUMM . . . to the above mentioned drugs but could also be used to include any other drug which displays suitable amphiphilic and **emulsion** -stabilizing properties.

SUMM A conventional pharmacologically inert oil is included as a component in the formulation when the **emulsion**-stabilizing drug is not itself used as the internal oil phase.

SUMM . . . surfactant is included as a component in the formulation when the drug functions as the internal oil phase of the **emulsion**.

SUMM By means of the present invention the undesirable properties of both the parenteral and the **oral** dosage form, mentioned in the background of the invention, can be avoided. Certain compounds, because of their chemical stucture, have. . . fundamental changes in the nature of the interface which are of considerable importance in different contexts. For example, in an **emulsion** the adsorption of a surfactant at the oil-water interface lowers the interfacial tension thereby aiding in the dispersal of the. . . allow storage for a long period of time (typically two years) of pharmaceutically interesting two-phase systems such as for example **emulsions**. The geometrical shape of the amphiphilic molecule and the presence of any substituents in said molecule can have an appreciable effect on its stabilizing properties. Surprisingly, it has been found that e.g. CMZ and said analogues display excellent **emulsion**-stabilizing properties which allow **emulsions** of these compounds to be stored for a long period of time. Due to the geometrical shape and the amphiphilic properties of the drug molecule it is adsorbed at the surface of the droplets in the **emulsion**, forming a rigid and tightly packed interfacial film thereby reducing the possibility of collisions leading to droplet coalescence and consequently. . .

SUMM . . . number of other drugs with hydrophobic portions comprising aromatic and/or heterocyclic ring systems or a steroid skeleton also display good **emulsion**-stabilizing properties.

SUMM Examples of the types of drugs, besides CMZ and its analogues, which have been found beneficial to use as **emulsion**-stabilizing agents include: antidepressants, neuroleptics, immunosuppressants, immunomodulators, antibiotics, antiinflammatory agents, proton pump inhibitors, calcium channel blockers, such as felodipine, and beta. . .

SUMM . . . usually observed that mixtures of conventional surfactants form even more stable systems than do single surfactants, even with very dilute **emulsions**, it has in some cases been found beneficial to use **emulsion**-stabilizing surface active drugs as co-surfactants together with any conventional pharmaceutically acceptable non-ionic surfactants, such as the poloxamers F68, F127 or. . .

SUMM . . . used by a person skilled in the art it is possible to manufacture a stable two-phase system like e.g. an **emulsion** of

any appropriate drug mentioned above, where the stabilizing effect is due to the surface active drug alone or the. . . any other appropriate drug which is in the liquid state, could also function as the actual oil phase in an **emulsion** system in that way making it possible to incorporate a high concentration of the drug. In the latter case said. . .

DRWD FIG. 1A shows the .sup.13 C-NMR spectra of an **emulsion** with CMZ;

DRWD FIG. 1B shows the .sup.13 C-NMR spectra of an **emulsion** without CMZ;

DRWD . . . 2 shows changes in the chemical shifts of the carbonyl carbons of a phospholipid, located at the interface in the **emulsion** system, in the presence of CMZ; and

DETD . . . formulation in the former case can be established by known techniques such as .sup.13 C-NMR and a spectra of an **emulsion** with and without CMZ is shown in FIG. 1. Using .sup.13 C-NMR chemical shift determinations, it is possible to obtain information on the location of the CMZ-molecule in the **emulsion** system. For example, according to FIG. 2 the chemical shifts of the carbonyl carbons of a phospholipid, which are located at the interface in the **emulsion** system, is changed in the presence of CMZ. In fact, there is a linear relationship between the concentration of CMZ. . . of the carbonyl carbons (FIG. 2). The chemical shifts of the methylene carbons, being located in the core of the **emulsion** droplets is essentially unaffected by the presence of CMZ which can also be seen in FIG. 2. Notably, the effects. . . its immediate environment (.ltoreq.5 .ANG.), these findings clearly show that CMZ is primarily located in the surface region of the **emulsion** droplets.

DETD Surprisingly, it has been found that the presence of **emulsion**-stabilizing surface active drugs at the interface of an **emulsion** not only produces **emulsions** with excellent physical stability but also makes it possible to improve poor chemical stability of the drug in some cases,. . . any other appropriate drug which is in the liquid state has been used as the actual oil phase of an **emulsion**, thus allowing for a prolonged storage at room temperature. It has also become possible to substantially increase the drug concentration. . . Hence, the safety of e.g. CMZ in the clinic was improved by a substantially reduced sorption of the drug by **intravenous** infusion giving sets and moreover by giving the **emulsion** orally it was found that this type of formulation was also capable of improving the conventional liquid **oral** dosage form by a considerably better masking of the bitter taste of CMZ and at the same time solving the. . .

DETD in the case where the **emulsion**-stabilizing surface active drug is not itself used as the internal oil phase by

DETD adding the **emulsion**-stabilizing surface active drug and an optional conventional surfactant to a two-phase, oil-water-system at room temperature;

DETD allowing the **emulsion**-stabilizing surface active drug or the **emulsion**-stabilizing surface active drug together with the conventional surfactant to equilibrate at the interface;

DETD homogenizing by high pressure technique whereby a stable **emulsion** is obtained which has a droplet size distribution where the main fraction is below 200 nm;

DETD dispersing the **emulsion**-stabilizing surface active drug together with a conventional surfactant in water at room temperature;

DETD homogenizing by high pressure technique; whereby a stable **emulsion** is obtained which has a droplet size distribution where

the main fraction is below 200 nm.

DETD This novel formulation comprises in general the **emulsion**-stabilizing surface active drug in a concentration from about 0.01 to 5% w/v.

DETD More particularly, the novel formulation of the invention comprises: a) the **emulsion**-stabilizing surface active drug in an amount of from about 0.01 to 5.0 g per 100 ml of the final formulation;. . . such as soybean oil, safflower oil, sesame oil, peanut oil, cottonseed oil, borago oil, sunflower oil, corn oil, olive oil, **medium chain triglycerides** (such as Miglyol.RTM.), or acetylated monoglycerides; c) a surfactant in an amount of from about 0.1 to 20 g per. . .

DETD The administration in the novel method of treatment of this invention may conveniently be **oral** or parenteral at a dosage level of, for example, about 1 to 3000 mg/kg, preferably about 10 to 1000 mg/kg. . . 1 to 4 doses or treatments per day. The dose will depend on the route of administration preferred routes being **oral** or **intravenous** administration. It will be appreciated that the severity of the disease, the age of the patient and other factors normally. . .

DETD Oil-in-water **emulsions** of CMZ for **intravenous** and **oral** use were prepared from the following components:

DETD In a first step the **emulsion**-stabilizing drug and a surfactant were added to a two-phase system, oil-water, at room temperature and were subsequently allowed to equilibrate at the interface. This formulation, together with additional indicated components in the formula, was homogenized and the resulting **emulsion** was stable and had an average droplet size below 100 nm and could easily be sterile filtered (200 nm filter).

DETD Oil-in-water **emulsions** were prepared as described in Examples 1-2 with the following components:

DETD Oil-in-water **emulsions** were prepared as described in Examples 1-2 with the following components:

DETD Oil-in-water **emulsions**, according to Examples 9-12, were prepared with the only difference that a sodium carbonate buffer pH 7.0 was used to. . .

DETD Oil-in-water **emulsions** were prepared as described in Examples 1-2 with the following components:

DETD Oil-in-water **emulsions** were prepared according to Examples 17-20 with the only difference that a sodium carbonate buffer pH 7.0 was used to. . .

DETD Oil in water **emulsions**, where the **emulsion**-stabilizing drug was used as the sole stabilizing agent in the system, were prepared from the following components:

DETD In a first step the **emulsion**-stabilizing drug was added to a two-phase system, oil-water, at room temperature and was subsequently allowed to equilibrate at the interface. This formulation, together with additional indicated components in the formula, was homogenized and the resulting **emulsion** was stable and had an average droplet size below 100 nm and could easily be sterile filtered (200 nm filter).

DETD Oil in water **emulsions** were prepared as described in Examples 25-26 with the following components:

DETD **Emulsions** where the drug functions as the internal oil-phase of the system were prepared from the following components:

DETD In a first step the drug was dispersed in water at room temperature. An **emulsion** was then prepared from the resulting drug-water dispersion, together with additional indicated components in the

formula. The resulting **emulsion** was stable and had an average droplet size below 100 nm and could easily be sterile filtered (200 nm filter).

DETD **Emulsions** according to Examples 31-32 were prepared with the following components:

DETD **Emulsions** according to Examples 31-32 were prepared with the following components:

DETD **Emulsions** according to Examples 39-42 were prepared with the only difference that a sodium carbonate buffer pH 7.0 was used to. . .

CLM What is claimed is:

1. A process for the preparation of a pharmaceutical formulation in the form of an oil-in-water **emulsion** comprising the steps of: (a) in the case where an **emulsion**-stabilizing surface active drug is not itself used as the internal oil phase, (i) adding the **emulsion**-stabilizing surface active drug and an optimal conventional surfactant to a two-phase, oil-water system at room temperature; (ii) allowing the **emulsion**-stabilizing surface active drug or the **emulsion**-stabilizing surface active drug together with the conventional surfactant to equilibrate at an interface of oil and water; (iii) adding an agent giving isotonicity to the final formulation; and (iv) homogenizing by high pressure technique; whereby a stable **emulsion** is-obtained which has a droplet size distribution where the main fraction is below 200 nm; or (b) in the case where the drug functions as the internal oil phase of the system, (i) dispersing the **emulsion**-stabilizing surface active drug together with a conventional surfactant in water at room temperature; (ii) allowing the surfactant to equilibrate at. . . (iii) adding an agent giving isotonicity to the final formulation; and (iv) homogenizing by high pressure technique; whereby a stable **emulsion** is obtained which has a droplet size distribution where the main fraction is below 200 nm.

```
=> s medium chain triglyceride? and babassu oil
L18         30 MEDIUM CHAIN TRIGLYCERIDE? AND BABASSU OIL

=> s dementia and alzheimer
L19      18369 DEMENTIA AND ALZHEIMER

=> s l18 and l19
L20          0 L18 AND L19

=> s dementia
L21      50462 DEMENTIA

=> s l21 and l18
L22          0 L21 AND L18

=> s alzheimer
L23      60797 ALZHEIMER

=> s l18 and l23
L24          0 L18 AND L23
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=> s medium chain triglyceride? or coconut oil
L25      27138 MEDIUM CHAIN TRIGLYCERIDE? OR COCONUT OIL

=> s l25 and l23
L26        574 L25 AND L23

=> s l21 and l26
L27        383 L21 AND L26

=> s l27 and py<2000
   1 FILES SEARCHED...
L28        285 L27 AND PY<2000

=> dup rem l28
PROCESSING COMPLETED FOR L28
L29         285 DUP REM L28 (0 DUPLICATES REMOVED)

=> s emulsion and oral and intravenous and l29
L30        117 EMULSION AND ORAL AND INTRAVENOUS AND L29

=> s l30 and neuronal
L31         33 L30 AND NEURONAL

=> d l31 1-33 ab bib kwic

L31  ANSWER 1 OF 33  USPATFULL
AB     A compound, or a solvate or a salt thereof, of formula (I), wherein, Ar
       is an optionally substituted aryl or a C.sub.5-7 cycloalkdienyl group,
       or an optionally substituted single or fused ring aromatic heterocyclic
       group; R, R.sub.1, R.sub.2 and R.sub.3 are as defined in the
       description; a process for the preparation of such a compound, a
       pharmaceutical composition containing such a compound or composition in
       medicine. ##STR1##
AN     2001:136665  USPATFULL
TI     Quinoline derivatives
IN     Giardina, Giuseppe Arnaldo Maria, Milan, Italy
       Grugni, Mario, Verbania, Italy
       Raveglia, Luca Francesco, Milan, Italy
       Farina, Carlo, Milan, Italy
PA     SmithKline Beecham S.p.A., Milan, Italy (non-U.S. corporation)
PI     US 6277862         B1   20010821
       WO 9721680  19970619                                          <--
AI     US 1998-77151           19980522 (9)
       WO 1996-EP5203          19961122
                               19980522  PCT 371 date
                               19980522  PCT 102(e) date
PRAI   IT 1995-MI2461      19951124
       IT 1996-MI1689      19960802
DT     Utility
FS     GRANTED
EXNAM  Primary Examiner: Seaman, D. Margaret
LREP   Stein-Fernandez, Nora, Venetianer, Stephen, Kinzig, Charles M.
CLMN   Number of Claims: 29
ECL    Exemplary Claim: 1
DRWN   No Drawings
LN.CNT 2231
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI     US 6277862         B1   20010821
       WO 9721680  19970619                                          <--
SUMM   . . . such as systhemic lupus erythematosis; gastrointestinal (GI)
```

disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and urinary incontinence; renal disorders and disorders of the bladder function,. . .

SUMM . . . of disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related **dementia**, senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease, Down's syndrome, Huntington's disease, Parkinson's disease, movement disorders and convulsive disorders (for example epilepsy); demyelinating diseases such as multiple. . .

SUMM . . . a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for **oral**, rectal, topical, parenteral, **intravenous** or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

SUMM The compositions, for example those suitable for **oral** administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for. . .

SUMM Compositions for **oral** administration as liquids may be in the form of, for example, **emulsions**, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before. . . for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated **coconut oil**, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for. . .

SUMM The compounds of this invention may also be administered by a non-**oral** route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or **emulsion** in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The. . .

SUMM The compounds of this invention may also be administered by inhalation, via the nasal or **oral** routes. Such administration can be carried out with a spray formulation comprising a compound of the invention and a suitable. . .

CLM What is claimed is:

. . . GI tract; renal disorders and disorders of the bladder function, disorders of the central nervous system; neurodegenerative disorders of the **Alzheimer** type, **Alzheimer**'s disease, Down's syndrome, Huntington's; demyelinating diseases and other neuropathological disorders; addiction disorders; stress related somatic disorders; reflex sympathetic dystrophy; dysthymic. . .

. . . of claim 11, wherein the GI disorders and diseases of the GI tract are selected from disorders associated with the **neuronal** control of viscera.

21. The method of claim 20, wherein the disorders associated with the **neuronal** control of viscera are selected from ulcerative colitis, Crohn's disease and urinary incontinence.

23. The method of claim 11, wherein the neurodegenerative disorders are selected from AIDS related **dementia**, senile **dementia**

of the **Alzheimer** type, **Alzheimer**'s disease, Down's syndrome, Huntington's disease, Parkinson's disease, movement disorders and convulsive disorders.

L31 ANSWER 2 OF 33 USPATFULL

AB A class of quinolinic sulfide derivatives of formula I are potent and specific antagonists at the strychnine insensitive glycine bitding site on the NMDA receptor complex with an pharmacological advantageous profile. They may be useful in treatment or prevention of neuro-degenerative disorders. Particularly, the compounds included in the present invention are especially useful for minimizing damage of the central nervous system arising as a consequence of ischemic or hypoxic condition such as stroke, hypoglycemia, cerebral ischemia, cardiac arrest, and physical trauma. They are also useful in prevention of chronic neurodegenerative disorders including epilepsy, **Alzheimer**'s disease, Huntington's disease and Parkinsonism. By virtue of their NMDA receptor antagonist properties, the present compounds may also use as anticonvulsant, analgesic, antidepressant, anxiolytic, and antischizophrenic agent. Formula I ##STR1## wherein R.sub.1, R.sub.2, R.sub.3, R.sub.4, and R are defined in specification.

AN 1999:151229 USPATFULL

TI Quinolinic sulfide derivatives acting as NMDA receptor antagonists and process for preparation thereof

IN Park, No Sang, Taejon-si, Korea, Republic of
Seong, Churl Min, Taejon-si, Korea, Republic of
Jung, Young Sik, Taejon-si, Korea, Republic of
Choi, Jin Il, Taejon-si, Korea, Republic of
Lee, Chang Woo, Taejon-si, Korea, Republic of
Chung, Yong Jun, Taejon-si, Korea, Republic of
Choi, Seung Won, Seoul, Korea, Republic of
Kong, Jae Yang, Taejon-si, Korea, Republic of
Park, Woo Kyu, Chungjoo-si, Korea, Republic of

PA Korea Research Institute of Chemical Technology, Taejon-si, Korea, Republic of (non-U.S. corporation)

PI US 5990126 19991123 <--

AI US 1998-52752 19980331 (9)

PRAI KR 1997-11958 19970331
KR 1997-13818 19970415
KR 1997-58546 19971106

DT Utility

FS Granted

EXNAM Primary Examiner: Kight, John; Assistant Examiner: Aulakh, Charanjit S.

LREP Dilworth & Barrese

CLMN Number of Claims: 16

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 2336

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5990126 19991123 <--

AB . . . hypoglycemia, cerebral ischemia, cardiac arrest, and physical trauma. They are also useful in prevention of chronic neurodegenerative disorders including epilepsy, **Alzheimer**'s disease, Huntington's disease and Parkinsonism. By virtue of their NMDA receptor antagonist properties, the present compounds may also use as. . .

SUMM They are also useful in prevention of chronic neuro-degenerative disorders including epilepsy, **Alzheimer**'s disease, Huntington's disease and Parkinsonism.

SUMM . . . health care and social support systems because of the increase

in the incidence of chronic, degenerative illness such as senile **dementia**. Approximately 4 millions individuals over the age of 65 in the United States (or 15% of the population) has some degree of **dementia**, Two thirds of them(over 2.5 millions) are affected severely, remain home sitting and relying on family and community resources for their care. Approximately 55% of all case of **dementia** are known as **Alzheimer**'s disease. The **Alzheimer**'s disease patient gradually loses verbal communication skills, as evidenced by decreased ability to relate words to objects and impaired comprehension of their verbal output. Recent research efforts provide some information about the underlying pathophysiology of this illness of **dementia**. And of several causal theories, the major plausible hypothesis are based on the fact that differentiation, growth, and degeneration of. . .

SUMM The amino acid L-glutamate is the most important fast excitatory neurotransmitter in **neuronal** circuits in the mammalian central nervous system(CNS). Almost all CNS neurons can be excited by L-glutamate, acting on a variety. . .

SUMM . . . brain and spinal cord, are cell surface protein complex that is involved in excitatory synaptic transmission and the regulation of **neuronal** growth.

SUMM Direct treatment of glutamate in vitro to cultured **neuronal** cells results in rapid cellular swelling followed by delayed toxicity over the subsequent 24 hours. This excitotoxicity has been shown to be Ca.sup.2+ dependent. Following **neuronal** trauma a large Ca.sup.2+ influx into the neuron through gated ion channel, such as glutamate receptors, initiates a cascade of. . . feedback to accelerate the release of glutamate and excitotoxicity. Among these events are activation of proteases and lipases, breakdown of **neuronal** membranes and formation of free radical, and ultimately, cell death [J. W. Mcdold, M. V. Johnson, Brain Res, Reviews 15,. . .

SUMM . . . clinical indications including ischemia and epilepsy. They may also be useful in the prevention of chronic neurodegenerative disorders such as **Alzheimer**'s disease, Huntington's disease and Parkinsonism [G.Johnson, Annu. Rep. Med. Chem. 24, 41 (1989); G. Johnson and C. F. Bigge, ibid.. . . is also believed to be central to the concept of long term potentiation (LTP), which is the persistent strengthening of **neuronal** connections that underlie learning and memory.

SUMM . . . hypoglycemia, cerebral ischemia, cardiac arrest, and physical trauma. They are also useful in prevention of chronic neurodegenerative disorders including epilepsy, **Alzheimer**'s disease, Huntington's disease and Parkinsonism. By virtue of their NMDA receptor antagonist properties, the present compounds may also use as. . .

SUMM . . . invention are preferably in unit dosage forms such as tablets, capsules, powders, granules, sterile solutions or suspensions, or suppositories, for **oral**, **intravenous**, parenteral or rectal administration. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical. . . be incorporated for administration orally or by injection include aqueous solutions, suitably, flavoured syrups, aqueous or oil suspensions, and flavoured **emulsions** with edible oils such as cotton-seed oil, sesame oil, **coconut oil** or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable

dispersing or suspending agents for aqueous suspensions include. . . a regimen of 1 to 4 times per day. In a particular embodiment, the compounds may be conveniently administered by **intravenous** infusion.

DETD The compounds of the present invention are also useful in prevention of chronic neurodegenerative disorders including epilepsy, **Alzheimer**'s disease, Huntington's disease and Parkinsonism. By virtue of their NMDA receptor antagonist properties, the present compounds may also use as. . .

CLM What is claimed is:
13. The method for treatment of epilepsy, stroke, **Alzheimer**'s disease, Huntington's disease and Parkinsonism comprising administering a composition as defined in claim 1.

L31 ANSWER 3 OF 33 USPATFULL

AB A method for the treatment of cerebrovascular disorders and/or disorders associated with cerebral senility and/or allergic disorders, proliferative skin disorders, and bronchodilation which method comprises the administration of an effective, non-toxic amount of a compound of formula (I): ##STR1## or if appropriate a pharmaceutically acceptable salt thereof, wherein R.sup.1 and R.sup.2 each independently represent alkyl or a moiety of formula (a):

--(CH.sub.2).sub.m --A (a)

wherein m represents zero or an integer 1, 2 or 3; A represents a substituted or unsubstituted cyclic hydrocarbon radical; and

R.sup.3 represents a halogen atom, a nitro group, or a group --NR.sup.4 R.sup.5 wherein R.sup.4 and R.sup.5 each independently represents hydrogen, alkyl or alkylcarbonyl or R.sup.4 and R.sup.5 together with the nitrogen to which they are attached forming an optionally substituted, heterocyclic group; certain novel compounds falling within formula (I) and compositions comprising such compounds.

AN 1999:141942 USPATFULL

TI Substituted xanthines and their use in the treatment of cerebrovascular disorders and other diseases

IN Spicer, Barbara Ann, Epsom, United Kingdom
Smith, Harry, Epsom, United Kingdom
Maschler, Harald, Nordstremmen, Germany, Federal Republic of

PA SmithKline Beecham p.l.c., Brentford, United Kingdom (non-U.S. corporation)

PI US 5981535 19991109 <--

AI US 1995-474093 19950607 (8)

RLI Continuation of Ser. No. US 1995-379092, filed on 26 Jan 1995, now abandoned which is a continuation of Ser. No. US 1993-28765, filed on 9 Mar 1993, now abandoned which is a continuation of Ser. No. US 1990-497992, filed on 23 Mar 1990, now abandoned

PRAI GB 1989-6792 19890323

DT Utility

FS Granted

EXNAM Primary Examiner: Berch, Mark L.

LREP Dinner, Dara L., Venetianer, Stephen, Kinzig, Charles M.

CLMN Number of Claims: 38

ECL Exemplary Claim: 1,2,6,9

DRWN No Drawings

LN.CNT 1178

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5981535 19991109 <--
SUMM . . . improve data acquisition or retrieval following transient forebrain ischaemia and are therefore useful in the treatment of cerebral vascular and **neuronal** degenerative disorders associated with learning, memory and cognitive dysfunctions including cerebral senility, multi-infarct **dementia**, senile **dementia** of the **Alzheimer** type, age associated memory impairment and certain disorders associated with Parkinson's disease.
SUMM These compounds are also indicated to have neuroprotectant activity. They are therefore useful in the prophylaxis of disorders associated with **neuronal** degeneration resulting from ischaemic events, including cerebral ischaemia due to cardiac arrest, stroke and also after cerebral ischaemic events such. . .
SUMM . . . a method for the treatment of cerebrovascular disorders and/or disorders associated with cerebral senility and/or prophylaxis of disorders associated with **neuronal** degeneration resulting from ischaemic events and/or peripheral vascular disease and/or proliferative skin disease and/or for disorders of the respiratory tract. . .
SUMM . . . a medicament for the treatment of cerebrovascular disorders and/or disorders associated with cerebral senility and/or prophylaxis of disorders associated with **neuronal** degeneration resulting from ischaemic events and/or peripheral vascular disease and/or proliferative skin diseases and/or disorders of the respiratory tract and/or. . .
SUMM . . . for use in the treatment of cerebrovascular disorders and/or disorders associated with cerebral senility and/or prophylaxis of disorders associated with **neuronal** degeneration resulting from ischaemic events and/or peripheral vascular disease and/or proliferative skin diseases and/or disorders of the respiratory tract and/or. . .
SUMM . . . a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for **oral**, rectal, topical, parenteral, **intravenous** or intramuscular administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.
SUMM . . . be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as **oral** or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.
SUMM Unit dose presentation forms for **oral** administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin,. . .
SUMM The solid **oral** compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used. . .
SUMM **Oral** liquid preparations may be in the form of, for example, **emulsions**, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before. . . agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated **coconut oil**, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or. . .
CLM What is claimed is:
17. The unit dose composition according to claim 16 formulated for

oral, topical, rectal, or parenteral administration.

L31 ANSWER 4 OF 33 USPATFULL
AB FK506 and geldanamycin promote nerve regeneration by a common mechanism that involves the binding of these compounds to polypeptide components of steroid receptor complexes other than the steroid hormone binding portion of the complex (FKBP52 and hsp90, respectively). These and other agents cause hsp90 dissociation from steroid receptor complexes or block association of hsp90 with steroid receptor complexes.
AN 1999:128537 USPATFULL
TI Compositions and methods for promoting nerve regeneration
IN Gold, Bruce G., West Linn, OR, United States
PA Orgegon Health Sciences University, Portland, OR, United States (U.S. corporation)
PI US 5968921 19991019 <--
AI US 1997-956691 19971024 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Weddington, Kevin E.
LREP Klarquist Sparkman Campbell Leigh & Whinston, LLP
CLMN Number of Claims: 36
ECL Exemplary Claim: 1
DRWN 15 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 1254
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5968921 19991019 <--
DETD . . . the hip. Following the sciatic nerve crush, the test compound is administered to the rats, e.g., by subcutaneous injection or **oral** administration. Functional recovery is assessed by determining the number of days following nerve crush until the animal demonstrates onset of. . .
DETD . . . including increasing penetration of the analogs into a given cellular compartment (e.g., blood, lymphatic system, central nervous system, etc.), increase **oral** availability, increase solubility to permit administration by injection, alter metabolism, and alter rate of excretion, for example.
DETD . . . dosage levels are between about 0.1 to about 400 mg/kg per day of the FK506 analog for subcutaneous delivery. For **oral** administration, preferred dosage levels are between about 0.01 to about 40 mg/kg/day.
DETD . . . invention can be periodically administered to a mammalian patient (e.g., a human patient), in need of such treatment, to promote **neuronal** regeneration and functional recovery and to stimulate neurite outgrowth and thereby to treat various neuropathological states, including damage to peripheral. . . syndromes, peripheral neuropathies such as those caused by lead, acrylamides, gamma-diketones (glue-sniffer's neuropathy), carbon disulfide, dapsone, ticks, porphyria, Gullain-Barre syndrome, **Alzheimer**'s disease, Parkinson's disease, and Huntington's chorea.
DETD . . . 206:81-84, 1996; Drake et al., Acta. Physiol. Scand. 158:155-159, 1996; and Kuroda et al., Neurosci. Res. Comm. 19:83-90, 1996), AIDS **dementia** (see, e.g., Dawson and Dawson, Adv. Neuroimmunol. 4:167-173, 1994; and Sekigawa et al., J. Clin. Immunol. 15:312-317, 1995); hair growth. . .
DETD The compositions can be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as **oral**,

topical, or sterile parenteral solutions or suspensions (e.g., eye or ear drops, throat or nasal sprays, etc.), transdermal patches, and. . .

DETD . . . inhalation spray, or via an implanted reservoir. The term "parenterally" as used herein includes, but is not limited to subcutaneous, **intravenous**, intramuscular, intrasternal, intrasynovial, intrathecal, intrahepatic, intralesional, and intracranial administration, for example, by injection or infusion. For treatment of the central. . .

DETD Tablets and capsules for **oral** administration can be in a form suitable for unit dose presentation and can contain conventional pharmaceutically acceptable excipients. Examples of. . . agents, such as sodium lauryl sulfate. The tablets can be coated according to methods well known in normal pharmaceutical practice. **Oral** liquid preparations can be in the form of, for example, aqueous or oily suspensions, solutions, **emulsions**, syrups or elixirs, or can be presented as a dry product for reconstitution with water or other suitable vehicle before. . . hydrogenated edible fats, emulsifying agents, e.g., lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (including edible oils), e.g., almond oil, fractionated **coconut oil**, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives such as methyl or propyl p-hydroxybenzoate or sorbic acid,. . .

L31 ANSWER 5 OF 33 USPATFULL

AB The present invention is directed to certain novel compounds represented by structural formula I: ##STR1## or a pharmaceutically acceptable salt thereof, wherein R.sup.3, R.sup.6, R.sup.7, R.sup.8, R.sup.11, R.sup.12, R.sup.13, A, m, n and the dashed lines are defined herein. The invention is also concerned with pharmaceutical formulations comprising these novel compounds as active ingredients and the use of the novel compounds and their formulations in the treatment of certain disorders. The compounds of this invention are tachykinin receptor antagonists and are useful in the treatment of inflammatory diseases, pain or migraine, asthma and emesis.

AN 1999:85445 USPATFULL

TI Heteroaryl spiroethercycloalkyl tachykinin receptor antagonists

IN Durette, Philippe, New Providence, NJ, United States
Kopka, Ihor, Millburn, NJ, United States
MacCoss, Malcolm, Freehold, NJ, United States
Mills, Sander, Scotch Plains, NJ, United States

PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

PI US 5929094 19990727 <--

AI US 1997-956181 19971022 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Rotman, Alan L.; Assistant Examiner: Aulakh, Charanjit S.

LREP Thies, J. Eric, Rose, David L.

CLMN Number of Claims: 13

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 3849

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5929094 19990727 <--
SUMM Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, **Alzheimer**'s disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases. . . al., Eur. J. Pharmacol., 249, R3-R4 (1993), F. D. Tattersall, et al., Neuropharmacology, 33, 259-260 (1994)], vasodilation, bronchospasm, reflex or **neuronal** control of the viscera [Mantyh et al., PNAS, 85, 3235-9 (1988)] and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes [Yankner et al., Science, 250, 279-82 (1990)] in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic. . .

SUMM . . . may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as **dementia**, including senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and. . . disorders, and diseases of the GI tract, such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, nausea, and emesis, including acute, delayed, post-operative, late-phase,. . .

SUMM . . . or treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, broncho-pneumonia,. . . as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain. . .

SUMM . . . conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for **oral** administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

SUMM . . . active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, **emulsions**, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia,. . .

SUMM . . . may be incorporated for administration orally or by injection include aqueous solution, suitably flavoured syrups, aqueous or oil suspensions, and **emulsions** with acceptable oils such as cottonseed oil, sesame oil, **coconut oil** or peanut oil, or with a solubilizing or emulsifying agent suitable for **intravenous** use, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and. . .

SUMM . . . or solid compositions may contain suitable pharmaceutically

acceptable excipients as set out above. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by. . .

SUMM . . . unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, **intravenous**, intramuscular, intrasternal injection or infusion techniques.

L31 ANSWER 6 OF 33 USPATFULL

AB Substituted heterocycles of the general structural formula: ##STR1## are

tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma and emesis, and calcium channel blockers useful in the treatment of cardiovascular conditions such as angina, hypertension or ischemia.

AN 1999:78711 USPATFULL

TI Morpholine and thiomorpholine tachykinin receptor antagonists

IN Dorn, Conrad P., Plainfield, NJ, United States
Hale, Jeffrey J., Westfield, NJ, United States
Maccoss, Malcolm, Freehold, NJ, United States
Mills, Sander G., Woodbridge, NJ, United States
Shah, Shrenik K., Metuchen, NJ, United States
Ladduwahetty, Tamara, Buckhurst Hill, United Kingdom

PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

PI US 5922706 19990713 <--

AI US 1997-969685 19971113 (8)

RLI Division of Ser. No. US 1995-525259, filed on 5 Sep 1995, now patented, Pat. No. US 5719147 which is a continuation-in-part of Ser. No. WO 1994-US14497, filed on 13 Dec 1994 And Ser. No. US 1993-169889, filed on

17 Dec 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-61914, filed on 19 May 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-971448, filed on 4 Nov 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-905976, filed on 29 Jun 1992, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Grumbling, Matthew V.

LREP Thies, J. Eric, Rose, David L.

CLMN Number of Claims: 21

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 7932

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5922706 19990713 <--

SUMM Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, **Alzheimer**'s disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases. . . al., Eur. J. Pharmacol., 249, R3-R4 (1993), F. D. Tattersall, et al., Neuropharmacology, 33, 259-260 (1994)], vasodilation, bronchospasm, reflex or **neuronal** control of the viscera [Mantyh et al., PNAS, 85 3235-9 (1988)] and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes [Yankner et al., Science, 250, 279-82 (1990)] in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic. . .

SUMM . . . may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as **dementia**, including senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and. . . disorders, and diseases of the GI tract, such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, nausea, and emesis, including acute, delayed, post-operative, late-phase,. . .

SUMM . . . or treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, broncho-pneumonia,. . . as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain. . .

SUMM . . . conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for **oral** administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

SUMM . . . ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, **emulsions**, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia,. . .

SUMM . . . may be incorporated for administration orally or by injection include aqueous solution, suitably flavoured syrups, aqueous or oil suspensions, and **emulsions** with acceptable oils such as cottonseed oil, sesame oil, **coconut oil** or peanut oil, or with a solubilizing or emulsifying agent suitable for **intravenous** use, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and. . .

SUMM . . . or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by. . .

SUMM . . . unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, **intravenous**, intramuscular, intrasternal injection or infusion techniques.

L31 ANSWER 7 OF 33 USPATFULL

AB In accordance with the present invention, there are provided conjugates of nitric oxide scavengers (e.g., dithiocarbamates, or "DC") and pharmacologically active agents (e.g., NSAIDs). Invention conjugates provide a new class of pharmacologically active agents (e.g., anti-inflammatory agents) which cause a much lower incidence of

side-effects due to the protective effects imparted by modifying the pharmacologically active agents as described herein. In addition, invention conjugates are more effective than unmodified pharmacologically active agents because cells and tissues contacted by the pharmacologically active agent(s) are protected from the potentially damaging effects of nitric oxide overproduction induced thereby as a result of the co-production of nitric oxide scavenger (e.g., dithiocarbamate), in addition to free pharmacologically active agent, when invention conjugate is cleaved.

AN 1999:72602 USPATFULL
TI Conjugates of dithiocarbamates with pharmacologically active agents and uses therefore
IN Lai, Ching-San, Encinitas, CA, United States
PA Medinox, Inc., San Diego, CA, United States (U.S. corporation)
PI US 5916910 19990629 <--
AI US 1997-869158 19970604 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Davis, Zinna Northington
LREP Reiter, Esq., Stephen E.Gray, Cary, Ware & Freidenrich
CLMN Number of Claims: 27
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1842
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5916910 19990629 <--

SUMM . . . ischemia, administration of cytokines, overexpression of cytokines, ulcers, inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease), diabetes, arthritis, asthma, **Alzheimer**'s disease, Parkinson's disease, multiple sclerosis, cirrhosis, allograft rejection, encephalomyelitis, meningitis, pancreatitis, peritonitis, vasculitis, lymphocytic choriomeningitis, glomerulonephritis, uveitis, ileitis, inflammation (e.g.,. . . distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, heart disease, atherosclerosis, dermatitis, urticaria, systemic lupus erythematosus, AIDA, AIDS **dementia**, chronic neurodegenerative disease, chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, migraine, Huntington's disease,. . .

SUMM . . . FK-506, FR-900506, Fujimycin, Prograf, IL-2 fusion toxin, and DAB.sub.389 IL-2), IL-4 antagonists (e.g., IL-4 fusion toxin, and DAB.sub.389 IL-4), immune-mediated **neuronal** damage inhibitors (e.g., NBI-114, NBI-115, and NBI-116), immunoglobins, immunostimulants (e.g., poly-ICLC, edelfosine, ALP, ET-18-OCH3, ET-18-OME, NSC-24, and poly-IC+poly-L-lysine+carboxymethylcellulose), immunosuppressants (e.g.,. . .

SUMM . . . hydrochloride, NSC-356894, NKT-01, Roquinimex, LS-2616, linomide, LJP-394, and CD-59 antigen), immunotoxins (e.g., Zolimomab aritox, xmmly-h65-rta, xomazyme-lym/CD5-Plus, OrthoZyme-CD5+, XomaZyme-H65-rta, Xomazyme-CD5 Plus), **intravenous** immunoglobulins (e.g., IVIG), integrin antagonists (e.g., integrin blockers), Migis.TM. antibodies, monoclonal antibody therapeutics, murine MAb (e.g., anti-SLE vaccine, and MAb. . .

SUMM **Alzheimer**'s disease agents, such as ACh release enhancers (e.g., T-588 (benzothiophene derivative)), acetylcholine release stimulants (e.g., DUP-996 and analogues), AMPA agonists. . .

SUMM . . . factors (e.g., Chiron/Ciba-Geigy compounds, Fujisawa compounds, and Genetech compounds), insulinotropins (e.g., Pfizer/Scios Nova

compounds), nerve growth factors (e.g., Genentech compounds), **oral** hypoglycemics (e.g., AS-6, glimepiride, Amaryl, CL 316,243, acarbose, miglitol, recombinant yeast glucagon, GlucaGen.TM., NovoNorm.TM., glipizide, insulinotropin, and CI-991/CS-045), platelet-derived growth. . .

SUMM . . . Fraxiparin), nafronyl/naftidrofuryl (e.g., Praxilene), nerve growth factor agonists (e.g., small molecule compounds, CNTF, BDNF,

2.5S

NGF, monosialoganglioside GM1, and Sigen/Sygen), **neuronal** calcium channel blockers (e.g., CPC-304, and CPC-317), **neuronal** differentiation compounds (e.g., F-spondin), neuropeptide agonists (e.g., Neurotrophic Peptide Trofexin), neutrophil inhibitory factors (e.g., small molecule compounds), nitric oxide agonists. . .

SUMM . . . a variety of pharmaceutically acceptable forms. For example, the scavenger can be delivered in the form of a solid, solution, **emulsion**, dispersion, micelle, liposome, and the like.

SUMM . . . are provided physiologically active composition(s) comprising compound(s) having the structure I in a suitable vehicle rendering said compound(s) amenable to **oral** delivery, transdermal delivery, **intravenous** delivery, intramuscular delivery, topical delivery, nasal delivery, and the like.

SUMM Pharmaceutical compositions of the present invention can be used in the form of a solid, a solution, an **emulsion**, a dispersion, a micelle, a liposome, and the like, wherein the resulting composition contains one or more of the compounds. . . active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, **emulsions**, suspensions, and any other form suitable for use. The carriers which can be used include glucose, lactose, gum acacia, gelatin,. . .

SUMM Pharmaceutical compositions containing the active ingredient may be in a

form suitable for **oral** use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, **emulsions**, hard or soft capsules, or syrups or elixirs. Compositions intended for **oral** use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such. . .

SUMM In some cases, formulations for **oral** use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid. . .

SUMM . . . may be employed including synthetic mono- or diglycerides, fatty acids (including oleic acid), naturally occurring vegetable oils like sesame oil, **coconut oil**, peanut oil, cottonseed oil, etc., or synthetic fatty vehicles like ethyl oleate or the like. Buffers, preservatives, antioxidants, and the. . .

CLM What is claimed is:

. . . for erythropoiesis stimulation, antiulcer/antireflux agents, antinauseants/antiemetics, septic shock agents, multiple sclerosis agents, organ transplantation agents, systemic lupus erythematosus

(SLE)

agents, **Alzheimer**'s disease agents, antiparkinson agents, psoriasis agents, diabetes agents, stroke agents, agents useful for the treatment of carcinomas, agents useful for. . .

20. A composition according to claim 19 wherein said pharmaceutically acceptable carrier is a solid, solution, **emulsion**, dispersion, micelle or liposome.

L31 ANSWER 8 OF 33 USPATFULL

AB The present invention is directed to certain novel compounds represented by structural formula I: ##STR1## or a pharmaceutically acceptable salt thereof, wherein R.sup.3, R.sup.6, R.sup.7, R.sup.8, R.sup.11, R.sup.12, R.sup.13, m, n and the dashed lines are defined herein. The invention is also concerned with pharmaceutical formulations comprising these novel compounds as active ingredients and the use of the novel compounds and their formulations in the treatment of certain disorders. The compounds of this invention are tachykinin receptor antagonists and are useful in the treatment of inflammatory diseases, pain or migraine, asthma and emesis.

AN 1999:27650 USPATFULL

TI Phenyl spiroethercycloalkyl tachykinin receptor antagonists

IN Caldwell, Charles G., Scotch Plains, NJ, United States
Chiang, Yuan-Ching, East Lyme, CT, United States
Dorn, Conrad, Plainfield, NJ, United States
Finke, Paul, Milltown, NJ, United States
Hale, Jeffrey, Westfield, NJ, United States
Maccoss, Malcolm, Freehold, NJ, United States
Mills, Sander, Scotch Plains, NJ, United States
Robichaud, Albert, Landenberg, PA, United States

PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

PI US 5877191 19990302 <--

AI US 1997-955898 19971022 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Richter, Johann; Assistant Examiner: Solola, Taofiq A.

LREP Thies, J. Eric, Rose, David L.

CLMN Number of Claims: 16

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 6950

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5877191 19990302 <--

SUMM Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, **Alzheimer**'s disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases. . . al., Eur. J. Pharmacol., 249, R3-R4 (1993), F. D. Tattersall, et al., Neuropharmacology, 33, 259-260 (1994)], vasodilation, bronchospasm, reflex or **neuronal** control of the viscera [Mantyh et al., PNAS, 85, 3235-9 (1988)] and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes [Yankner et al., Science, 250, 279-82 (1990)] in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic. . .

SUMM . . . may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as **dementia**, including senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and. . . disorders, and diseases of the GI tract, such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the **neuronal** control of viscera such

as ulcerative colitis, Crohn's disease, irritable bowel syndrome, nausea, and emesis, including acute, delayed, post-operative, late-phase,. . .

SUMM . . . or treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, broncho-pneumonia,. . . as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain. . .

SUMM . . . conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for **oral** administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

SUMM . . . ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, **emulsions**, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia,. . .

SUMM . . . may be incorporated for administration orally or by injection include aqueous solution, suitably flavoured syrups, aqueous or oil suspensions, and **emulsions** with acceptable oils such as cottonseed oil, sesame oil, **coconut oil** or peanut oil, or with a solubilizing or emulsifying agent suitable for **intravenous** use, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and. . .

SUMM . . . or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by. . .

SUMM . . . unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, **intravenous**, intramuscular, intrasternal injection or infusion techniques.

L31 ANSWER 9 OF 33 USPATFULL

AB Substituted heterocycles of the general structural formula: ##STR1## are tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma and emesis, and calcium channel blockers useful in the treatment of cardiovascular conditions such as angina, hypertension or ischemia.

AN 1999:22097 USPATFULL

TI Morpholine and thiomorpholine tachykinin receptor antagonists

IN Dorn, Conrad P., Plainfield, NJ, United States
Finke, Paul E., Milltown, NJ, United States
Hale, Jeffrey J., Westfield, NJ, United States
Maccoss, Malcolm, Freehold, NJ, United States
Mills, Sander G., Woodbridge, NJ, United States
Shah, Shrenik K., Metuchen, NJ, United States
Chambers, Mark Stuart, Watford, England

Harrison, Timothy, Great Dunmow, England
Ladduwahetty, Tamara, Buckhurst Hill, England
Williams, Brian John, Great Dunnow, England
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 5872116 19990216 <--
AI US 1997-959393 19971028 (8)
RLI Division of Ser. No. US 1995-525259, filed on 8 Sep 1995, now patented, Pat. No. US 5719147 And a continuation-in-part of Ser. No. US 1993-169889, filed on 17 Dec 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-61914, filed on 19 May 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-971448, filed on 4 Nov 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-905976, filed on 29 Jun 1992, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Weddington, Kevin E.
LREP Thies, J. Eric, Rose, David L.
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 8249
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5872116 19990216 <--
SUMM Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, **Alzheimer**'s disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases. . . al., Eur. J. Pharmacol., 249, R3-R4 (1993), F. D. Tattersall, et al., Neuropharmacology, 33, 259-260 (1994)], vasodilation, bronchospasm, reflex or **neuronal** control of the viscera [Mantyh et al., PNAS, 85, 3235-9 (1988)] and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes [Yankner et al., Science, 250, 279-82 (1990)] in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic. . .
SUMM . . . may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as **dementia**, including senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and. . . disorders, and diseases of the GI tract, such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, nausea, and emesis, including acute, delayed, post-operative, late-phase,. . .
SUMM . . . or treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, broncho-pneumonia,. . . as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's

disease and incontinence; disorders of blood flow caused by vasodilation; and pain. . .

SUMM . . . conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for **oral** administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

SUMM . . . active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, **emulsions**, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia,. . .

SUMM . . . may be incorporated for administration orally or by injection include aqueous solution, suitably flavoured syrups, aqueous or oil suspensions, and **emulsions** with acceptable oils such as cottonseed oil, sesame oil, **coconut oil** or peanut oil, or with a solubilizing or emulsifying agent suitable for **intravenous** use, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and. . .

SUMM . . . or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by. . .

SUMM . . . unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, **intravenous**, intramuscular, intrasternal injection or infusion techniques.

L31 ANSWER 10 OF 33 USPATFULL

AB Disclosed are spiro-substituted azacycles of formula (I), are tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, emesis and asthma. In particular compounds of formula (I) are shown to be neurokinin antagonists. ##STR1##

AN 1999:19160 USPATFULL

TI Spiro-substituted azacycles as tachykinin receptor antagonists

IN Hale, Jeffrey J., Westfield, NJ, United States
Maccoss, Malcolm, Freehold, NJ, United States
Mills, Sander G., Woodbridge, NJ, United States
Qi, Hongbo, Edison, NJ, United States
Shah, Shrenik K., Metuchen, NJ, United States

PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

PI US 5869496 19990209 <--
WO 9417045 19940804 <--

AI US 1995-481418 19950711 (8)
WO 1994-US819 19940125
19950711 PCT 371 date
19950711 PCT 102(e) date

DT Utility

FS Granted

EXNAM Primary Examiner: Rotman, Alan L.

LREP Rose, David L., Billups, Richard C.

CLMN Number of Claims: 16

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1976

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5869496 19990209 <--
WO 9417045 19940804 <--
SUMM . . . (1988) 141 (10) 3564-9 and A. Perianin, et al., Biochem. Biophys. Res. Commun. 161, 520 (1989)) vasodilation, bronchospasm, reflex or **neuronal** control of the viscera (Mantyh et al., PNAS (1988) 85 3235-9) and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes (Yankner et al., Science, (1990) 250, 279-82) in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic. . .
SUMM . . . include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related **dementia**, senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as. . . such as systemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of bladder function; fibrosing and collagen diseases such. . .
SUMM . . . unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, **intravenous**, intramuscular, intracisternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as
mice, rats, horses, cattle,. . .
SUMM The pharmaceutical compositions containing the active ingredient may be in a form suitable for **oral** use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, **emulsions**, hard or soft capsules, or syrups or elixirs. Compositions intended for **oral** use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such. . .
SUMM Formulations for **oral** use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent,. . .
SUMM . . . be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or **coconut oil**, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax,. . . cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable **oral** preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.
SUMM The pharmaceutical compositions of the invention may also be in the form
of oil-in-water **emulsions**. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for. . . example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan
monooleate. The **emulsions** may also contain sweetening and flavoring agents.

L31 ANSWER 11 OF 33 USPATFULL
AB Disclosed are Substituted azacycles of formula I ##STR1## are tachykinin

receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, and asthma. In particular compounds of formula I are shown to be neurokinin antagonists.

AN 1999:19153 USPATFULL
TI Trypthophan ureas as neurokinnin antagonists
IN Shah, Shrenik K., Metuchen, NJ, United States
Qi, Hongbo, Edison, NJ, United States
Maccoss, Malcolm, Freehold, NJ, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 5869489 19990209 <--
AI US 1997-814387 19970311 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Bernhardt, Emily
LREP Billups, Richard C., Panzer, Curtis C., Rose, David L.
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1140
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5869489 19990209 <--

SUMM . . . (1988) 141 (10) 3564-9 and A. Perianin, et al., Biochem. Biophys. Res. Commun. 161, 520 (1989)) vasodilation, bronchospasm, reflex or **neuronal** control of the viscera (Mantyh et al., PNAS (1988) 85, 3235-9) and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes (Yankner et al, Science, (1990) 250, 279-82) in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic. . .

SUMM . . . include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related **dementia**, senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as. . . such as systemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of bladder function; fibrosing and collagen diseases such. . .

SUMM . . . unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, **intravenous**, intramuscular, intracisternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as
mice, rats, horses, cattle,. . .

SUMM The pharmaceutical compositions containing the active ingredient may be in a form suitable for **oral** use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, **emulsions**, hard or soft capsules, or syrups or elixirs. Compositions intended for **oral** use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such. . .

SUMM Formulations for **oral** use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent,. . .

SUMM . . . be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or

coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax,. . . cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable **oral** preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

SUMM The pharmaceutical compositions of the invention may also be in the form of oil-in-water **emulsions**. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for. . . example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The **emulsions** may also contain sweetening and flavoring agents.

L31 ANSWER 12 OF 33 USPATFULL

AB The present invention is related to a pharmaceutical formulation which is an oil-in-water **emulsion** for parenteral and **oral** use which comprises

(i) an **emulsion**-stabilizing surface active drug in high concentration;

(ii) optionally a pharmacologically inert oil;

(iii) optionally a surfactant;

(iv) water or a buffer; and

(v) an agent giving isotonicity to the final formulation;

the use of and a process for preparation of the formulation.

AN 1998:150483 USPATFULL
TI **Emulsion** formulation
IN Lundquist, Stefan, Stockholm, Sweden
PA Astra Aktiebolag, Sweden (non-U.S. corporation)
PI US 5843465 19981201 <--
WO 9509609 19950413
AI US 1995-379486 19950130 (8)
WO 1994-SE926 19941005
19950130 PCT 371 date
19950130 PCT 102(e) date
PRAI SE 1993-3281 19931007
DT Utility
FS Granted
EXNAM Primary Examiner: MacMillan, Keith D.
LREP White & Case L.L.P.
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 597
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI **Emulsion** formulation
PI US 5843465 19981201 <--
WO 9509609 19950413
AB The present invention is related to a pharmaceutical formulation which is an oil-in-water **emulsion** for parenteral and **oral** use which comprises
AB (i) an **emulsion**-stabilizing surface active drug in high

concentration;

SUMM This invention relates to a novel pharmaceutical formulation comprising an **emulsion**-stabilizing surface active drug which may be administered parenterally or orally; and to the use of and a process for preparing. . .

SUMM . . . the CMZ-edisilate at room temperature (the product must be stored at +4.degree.-8.degree. C.) and the substantial sorption of CMZ by **intravenous** infusion giving sets. This sorption to plastics results in a safety problem in the clinic, especially when treating disorders requiring very accurate dosing. Finally, the **oral** liquid dosage form, a 5 w/v % syrup of CMZ-edisilate, also has a number of disadvantages such as poor stability. . .

SUMM . . . object of the invention is to provide a novel, clinically and pharmaceutically acceptable and useful formulation which is an oil-in-water **emulsion** for parenteral and **oral** use which comprises

SUMM (i) an **emulsion**-stabilizing surface active drug in high concentration;

SUMM The present invention is preferably related to **emulsion**-stabilizing surface active drugs having an anti-convulsant or sedative-hypnotic effect or drugs for preventing and/or treating neurodegeneration caused by acute and chronic neuropsychiatric disorders characterised by progressive processes that sooner or later lead to **neuronal** cell death and dysfunction. Such disorders include stroke; cerebral ischaemia; dysfunctions resulting from brain and/or spinal trauma; hypoxia and anoxia, such as from drowning, and including perinatal and neonatal hypoxic asphyxial brain damage; multi-infarct **dementia**; AIDS **dementia**; neurodegenerative diseases such as **Alzheimer**'s disease, Parkinson's disease, Huntington's chorea, epilepsy, multiple sclerosis and amytrophic lateral sclerosis; brain dysfunction in connection with surgery involving extracorporeal. . . to neurotoxins or radiation. This utility is manifested, for example, by the ability of the claimed formulation to inhibit delayed **neuronal** death in the gerbil bilateral occlusion model of ischaemia.

SUMM Preferred **emulsion**-stabilizing surface active drugs are the CMZ-base which is an oil at room temperature, and/or some analogues thereof which are oils. . . besides having a pharmacological effect, as a stabilizing surfactant or co-surfactant at the large interface in an oil in water **emulsion** system or in another aspect of the invention, functioning as the actual oil phase in an **emulsion** system.

SUMM . . . to the above mentioned drugs but could also be used to include any other drug which displays suitable amphiphilic and **emulsion**-stabilizing properties.

SUMM A conventional pharmacologically inert oil is included as a component in the formulation when the **emulsion**-stabilizing drug is not itself used as the internal oil phase.

SUMM . . . surfactant is included as a component in the formulation when the drug functions as the internal oil phase of the **emulsion**.

SUMM By means of the present invention the undesirable properties of both the parenteral and the **oral** dosage form, mentioned in the background of the invention, can be avoided. Certain compounds, because of their chemical structure, have. . . fundamental changes in the nature of the interface which are of considerable importance in different contexts. For example, in an **emulsion** the adsorption

of a surfactant at the oil-water interface lowers the interfacial tension thereby aiding in the dispersal of the. . . allow storage for a long period of time (typically two years) of pharmaceutically interesting two-phase systems such as for example **emulsions.** The geometrical shape of the amphiphilic molecule and the presence of any substituents in said molecule can have an appreciable effect on its stabilizing properties. Surprisingly, it has been found that e.g. CMZ and said analogues display excellent **emulsion**-stabilizing properties which allow **emulsions** of these compounds to be stored for a long period of time. Due to the geometrical shape and the amphiphilic properties of the drug molecule it is adsorbed at the surface of the droplets in the **emulsion,** forming a rigid and tightly packed interfacial film thereby reducing the possibility of collisions leading to droplet coalescence and consequently. . .

SUMM . . . number of other drugs with hydrophobic portions comprising aromatic and/or heterocyclic ring systems or a steroid skeleton also display good **emulsion**-stabilizing properties.

SUMM Examples of the types of drugs, besides CMZ and its analogues, which have been found beneficial to use as **emulsion**-stabilizing agents include: antidepressants, neuroleptics, immunosuppressants, immunomodulators, antibiotics, antiinflammatory agents, proton pump inhibitors, calcium channel blockers, such as felodipine, and beta. . .

SUMM . . . usually observed that mixtures of conventional surfactants form even more stable systems than do single surfactants, even with very dilute **emulsions,** it has in some cases been found beneficial to use **emulsion**-stabilizing surface active drugs as co-surfactants together with any conventional pharmaceutically acceptable non-ionic surfactants, such as the poloxamers F68, F127 or. . . used by a person skilled in the art it is possible to manufacture a stable two-phase system like e.g. an **emulsion** of any appropriate drug mentioned above, where the stabilizing effect is due to the surface active drug alone or the. . . any other appropriate drug which is in the liquid state, could also function as the actual oil phase in an **emulsion** system in that way making it possible to incorporate a high concentration of the drug. In the latter case said. . .

DRWD FIG. 1A shows the .sup.13 C-NMR spectra of an **emulsion** with CMZ;

DRWD FIG. 1B shows the .sup.13 C-NMR spectra of an **emulsion** without CMZ;

DRWD . . . the chemical shifts of the carbonyl carbons of a phospholipid, located at the interface between oil and water in the **emulsion** system, in the presence of CMZ; and

DETD . . . formulation in the former case can be established by known techniques such as .sup.13 C-NMR and a spectra of an **emulsion** with and without CMZ is shown in FIG. 1. Using .sup.13 C-NMR chemical shift determinations, it is possible to obtain information on the location of the CMZ-molecule in the **emulsion** system. For example, according to FIG. 2 the chemical shifts of the carbonyl carbons of a phospholipid, which are located at the interface in the **emulsion** system, is changed in the presence of CMZ. In fact, there is a linear relationship between the concentration of CMZ. . . of the carbonyl carbons (FIG. 2). The chemical shifts of the methylene carbons, being located in the core of the **emulsion** droplets is essentially unaffected by the presence of CMZ which can also be seen in

FIG. 2. Notably, the effects. . . immediate environment (.ltoreq.5 .ANG.), these findings clearly show that CMZ is primarily located in the surface region of the **emulsion** droplets.

DETD Surprisingly, it has been found that the presence of **emulsion** -stabilizing surface active drugs at the interface of an **emulsion** not only produces **emulsions** with excellent physical stability but also makes it possible to improve poor chemical stability of the drug in some cases,. . . any other appropriate drug which is in the liquid state has been used as the actual oil phase of an **emulsion**, thus allowing for a prolonged storage at room temperature. It has also become possible to substantially increase the drug concentration. . . Hence, the safety of e.g. CMZ in the clinic was improved by a substantially reduced sorption of the drug by **intravenous** infusion giving sets and moreover by giving the **emulsion** orally it was found that this type of formulation was also capable of improving the conventional liquid **oral** dosage form by a considerably better masking of the bitter taste of CMZ and at the same time solving the. . .

DETD in the case where the **emulsion**-stabilizing surface active drug is not itself used as the internal oil phase by

DETD adding the **emulsion**-stabilizing surface active drug and an optional conventional surfactant to a two-phase, oil-water-system at room temperature;

DETD allowing the **emulsion**-stabilizing surface active drug or the **emulsion**-stabilizing surface active drug together with the conventional surfactant to equilibrate at the interface;

DETD homogenizing by high pressure technique whereby a stable **emulsion** is obtained which has a droplet size distribution where the main fraction is below 200 nm;

DETD dispersing the **emulsion**-stabilizing surface active drug together with a conventional surfactant in water at room temperature;

DETD homogenizing by high pressure technique; whereby a stable **emulsion** is obtained which has a droplet size distribution where the main fraction is below 200 nm.

DETD This novel formulation comprises in general the **emulsion** -stabilizing surface active drug in a concentration from about 0.01 to 5% w/v.

DETD More particularly, the novel formulation of the invention comprises: a) the **emulsion**-stabilizing surface active drug in an amount of from about 0.01 to 5.0 g per 100 ml of the final formulation;. . . such as soybean oil, safflower oil, sesame oil, peanut oil, cottonseed oil, borago oil, sunflower oil, corn oil, olive oil, **medium chain triglycerides** (such as Miglyol.RTM.), or acetylated monoglycerides; c) a surfactant in an amount of from about 0.1 to 20 g per. . .

DETD The administration in the novel method of treatment of this invention may conveniently be **oral** or parenteral at a dosage level of, for example, about 1 to 3000 mg/kg, preferably about 10 to 1000 mg/kg. . . 1 to 4 doses or treatments per day. The dose will depend on the route of administration preferred routes being **oral** or **intravenous** administration. It will be appreciated that the severity of the disease, the age of the patient and other factors normally. . .

DETD Oil-in-water **emulsions** of CMZ for **intravenous** and **oral** use were prepared from the following components:

DETD In a first step the **emulsion**-stabilizing drug and a surfactant were added to a two-phase system, oil-water, at room temperature and were subsequently allowed to equilibrate at the interface. This

formulation, together with additional indicated components in the formula, was homogenized and the resulting **emulsion** was stable and had an average droplet size below 100 nm and could easily be sterile filtered (200 nm filter).

DETD Oil-in-water **emulsions** were prepared as described in Examples 1-2 with the following components:

DETD Oil-in-water **emulsions** were prepared as described in Examples 1-2 with the following components:

DETD Oil-in-water **emulsions**, according to Examples 9-12, were prepared with the only difference that a sodium carbonate buffer pH 7.0 was used to. . .

DETD Oil-in-water **emulsions** were prepared as described in Examples 1-2 with the following components:

DETD Oil-in-water **emulsions** were prepared according to Examples 17-20 with the only difference that a sodium carbonate buffer pH 7.0 was used to. . .

DETD Oil in water **emulsions**, where the **emulsion**-stabilizing drug was used as the sole stabilizing agent in the system, were prepared from the following components:

DETD In a first step the **emulsion**-stabilizing drug was added to a two-phase system, oil-water, at room temperature and was subsequently allowed to equilibrate at the interface. This formulation, together with additional indicated components in the formula, was homogenized and the resulting **emulsion** was stable and had an average droplet size below 100 nm and could easily be sterile filtered (200 nm filter).

DETD Oil in water **emulsions** were prepared as described in Examples 25-26 with the following components:

DETD **Emulsions** where the drug functions as the internal oil-phase of the system were prepared from the following components:

DETD In a first step the drug was dispersed in water at room temperature. An **emulsion** was then prepared from the resulting drug-water dispersion, together with additional indicated components in the formula. The resulting **emulsion** was stable and had an average droplet size below 100 nm and could easily be sterile filtered (200 nm filter).

DETD **Emulsions** according to Examples 31-32 were prepared with the following components:

DETD **Emulsions** according to Examples 31-32 were prepared with the following components:

DETD **Emulsions** according to Examples 39-42 were prepared with the only difference that a sodium carbonate buffer pH 7.0 was used to. . .

CLM What is claimed is:

1. A sterile pharmaceutical formulation of an oil-in-water **emulsion** for parenteral and **oral** administration which comprises: (i) an **emulsion**-stabilizing surface active drug in a concentration ranging from 0.01 g to 5.0 g per 100 ml of the final formulation;. . . an internal oil; (iv) water or a buffer; and (v) an agent giving isotonicity to the final formulation; the formulated **emulsion** having a major fraction of stable droplets having a size below 200 nm so as to be suitable for sterile. . .

2. The formulation according to claim 1 wherein the **emulsion**-stabilizing surface active drug is a drug for preventing neurodegeneration, treating neurodegeneration, or having an anti-convulsant or sedative-hypnotic effect.

3. The formulation according to claim 1 wherein the **emulsion** -stabilizing surface active drug is selected from the group consisting of 5-(2-chloroethyl)-4-methylthiazole, 5-(2-chloroethyl)-4-methyloxazole, 5-(2-chloroethyl)-2,4-dimethyloxazole, 5-(2-chloroethyl)-2,4-dimethylthiazole, 5-(2-chloro-1-hydroxyethyl)-4-methylthiazole and its optical isomers.

4. The formulation according to claim 3 wherein the **emulsion** -stabilizing surface active drug is 5-(2-chloroethyl)-4-methylthiazole.

. . . consisting of soybean oil, safflower oil, sesame oil, peanut oil, cottonseed oil, borago oil, sunflower oil, corn oil, olive oil, **medium chain triglycerides** and acetylated monoglycerides.

14. A sterile pharmaceutical **emulsion** preparation for parenteral or **oral** administration comprising an **emulsion**-stabilizing surface active drug in base form which is dispersed and equilibrated in a two-phase, oil-water-system which further comprises a pharmacologically. . . a sufficient amount of an agent for isotonicity; the preparation being homogenized under high pressure so as to obtain an **emulsion** which has a droplet size distribution where the main fraction is below 200 nm; and sterile filtered through a 0.2. . .

L31 ANSWER 13 OF 33 USPATFULL
AB Substituted heterocycles of the general structural formula: ##STR1## are
tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma, and emesis.
AN 1998:82754 USPATFULL
TI Morpholine compounds are prodrugs useful as tachykinin receptor antagonists
IN Dorn, Conrad P., Plainfield, NJ, United States
Hale, Jeffrey J., Westfield, NJ, United States
Maccoss, Malcolm, Freehold, NJ, United States
Mills, Sander G., Woodbridge, NJ, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 5780467 19980714 <--
AI US 1997-907738 19970808 (8)
RLI Division of Ser. No. US 1995-525870, filed on 8 Sep 1995, now patented, Pat. No. US 5691336 which is a continuation-in-part of Ser. No. US 1994-206771, filed on 4 Mar 1994, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Higel, Floyd D.
LREP Thies, J. Eric, Rose, David L.
CLMN Number of Claims: 19
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 7260
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5780467 19980714 <--
SUMM Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, **Alzheimer**'s disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases. . . al., Eur. J. Pharmacol., 249, R3-R4 (1993), F. D. Tattersall, et al., Neuropharmacology, 33, 259-260 (1994)], vasodilation, bronchospasm, reflex or **neuronal** control of the

viscera [Mantyh et al., PNAS, 85, 3235-9 (1988)] and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes [Yankner et al., Science, 250, 279-82 (1990)] in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic. . .

SUMM While all of the usual routes of administration are useful with the present compounds, the preferred routes of administration are **oral** and **intravenous**. After gastrointestinal absorption or **intravenous** administration, the present compounds are hydrolyzed or otherwise cleaved in vivo to the corresponding parent compounds of formula I, wherein. . .

SUMM . . . may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as **dementia**, including senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and. . . disorders, and diseases of the GI tract, such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, nausea, and emesis, including acute, delayed, post-operative, late-phase,. . .

SUMM . . . or treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, broncho-pneumonia,. . . as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain. . .

SUMM . . . conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for **oral** administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

SUMM . . . ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, **emulsions**, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia,. . .

SUMM . . . be incorporated for administration orally or by injection include aqueous solution, suitably flavoured syrups, aqueous or oil suspensions, and flavoured **emulsions** with edible oils such as cottonseed oil, sesame oil, **coconut oil** or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include. . .

SUMM . . . or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by. . .

SUMM . . . unit formulations containing conventional non-toxic

pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, **intravenous**, intramuscular, intrasternal injection or infusion techniques.

DETD . . . was partitioned between 40 mL of ethyl ether and 20 mL of water; mixing of the layers resulted in an **emulsion**. Centrifugation at 2800 rpm for 15 minutes broke the **emulsion**; the aqueous layer was separated and lyophilized to afford 188 mg (33%) of the compound tentatively identified as 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(4-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)-morpholine, dipotassium. . .

DETD . . . ether and air dried. The solid was partitioned between 150 mL of ethyl ether and 150 mL of water; an **emulsion** formed on mixing of the layers. The **emulsion** was transferred into 50 mL centrifuge tubes; centrifugation at 3000 rpm for 15 minutes caused separation of the layers. The. . .

L31 ANSWER 14 OF 33 USPATFULL

AB This invention relates to adenosine kinase inhibitors and to nucleoside analogs, C-4' modified pyrrolo[2,3-d]pyrimidine and pyrazolo[3,4-d]pyrimidine nucleoside analogs having activity as adenosine kinase inhibitors. The invention relates to nucleoside analogs of this kind, having zero substitutions or two substitutions at the C-4' position of the furanose (sugar) moiety. The invention also relates to the preparation and use of these adenosine kinase inhibitors in the treatment of cardiovascular, and cerebrovascular diseases, inflammation and other diseases which can be regulated by increasing the local concentration of adenosine.

AN 1998:65373 USPATFULL

TI C-4' modified adenosine kinase inhibitors

IN Boyer, Serge H., San Diego, CA, United States
Ugarkar, Bheemarao G., Escondido, CA, United States
Erion, Mark D., Del Mar, CA, United States

PA Metabasis Therapeutics, Inc., San Diego, CA, United States (U.S. corporation)

PI US 5763596 19980609 <--

AI US 1996-660505 19960607 (8)

RLI Continuation-in-part of Ser. No. US 1995-486161, filed on 7 Jun 1995, now patented, Pat. No. US 5674998 which is a continuation-in-part of Ser. No. US 1994-191282, filed on 3 Feb 1994, now patented, Pat. No. US 5506347 And Ser. No. US 1991-812916, filed on 23 Dec 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-647117, filed on 23 Jan 1991, now abandoned which is a continuation-in-part of Ser. No. US 1990-466979, filed on 18 Jan 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-408707, filed on 15 Sep 1989, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Wilson, James O.

LREP Darby & Darby

CLMN Number of Claims: 32

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 3099

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5763596 19980609 <--

SUMM . . . of an inhibitor by a factor of at least 10 and preferably at least 100 at pH values suitable for **intravenous** administration

(pH 4 to pH 10). In practice the use of salt form amounts to use of base
form; both. . .

DETD . . . of acute and chronic pain can be treated by administration of the compounds of the invention in a systemic or **oral** fashion, as illustrated by animal models detailed below.

DETD The compounds of the invention are also useful in the treatment of chronic neurodegenerative disease, such as **Alzheimer**'s disease, Parkinson's disease, ALS, Huntington's disease, and AIDS **dementia**.

DETD . . . autoclaved for 30 minutes, and stored at room temperature. Rats
were pretreated with vehicle or AK inhibitor (10 mg/kg) by **oral** gavage or i.p. administration and the volume of the left hind paw was measured using a water displacement plethysmometer (Stoelting Co., Wood Dale, Ill.). One hour after **oral** treatment or 30 minutes after i.p. treatment, the rats were briefly anaesthetized, and 0.1 ml of the carrageenan solution was. . .

DETD . . . The baseline paw volume was subtracted from the arthritic volumes to yield paw swelling. AK inhibitors were given by daily **oral** gavage beginning on day 4 after immunization, using polyethylene glycol-400 as the vehicle. Control rats received vehicle only. Percent inhibition. . .

DETD . . . nociceptors at the injection site while phase 2 behavior is thought to include a hyperalgesic component mediated by sensitization of
neuronal elements within the spinal cord. Studies from other laboratories have found the first portion of Phase 2 (sometimes referred
to. . .

DETD . . . Such rates are easily maintained when soluble compounds are intravenously administered as discussed below. When other methods are used (e.g., **oral** administration), use of time-release preparations to control the rate of release of the active ingredient may
be preferred. These compounds. . .

DETD . . . rectally in formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, **intravenous**, intramuscular, and intraarterial injections with a variety of infusion techniques. Intraarterial and **intravenous** injection as used herein includes administration through catheters. Preferred for certain indications are methods of administration which allow rapid access the tissue or organ being treated, such as **intravenous** injections for the treatment of myocardial infarction. When an organ outside a body
is being treated, perfusion is preferred.

DETD . . . compositions containing the active ingredient may be in any form suitable for the intended method of administration. When used for **oral** use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, **emulsions**, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for **oral** use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such. . .

DETD Formulations for **oral** use may be also presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent,. . .

DETD . . . be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or

coconut oil, or in a mineral oil such as liquid paraffin. The **oral** suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable **oral** preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

DETD The pharmaceutical compositions of the invention may also be in the form of oil-in-water **emulsions**. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as. . . such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The **emulsion** may also contain sweetening and flavoring agents.

DETD . . . will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for **oral** administration to humans may contain 20 to 1000 .mu.moles of active material compounded with an appropriate and convenient amount of. . . preferred that pharmaceutical composition be prepared which provides easily measurable amounts for administration. For example, an aqueous solution intended for **intravenous** infusion should contain from about 0.1 to about 15 .mu.moles of the active ingredient per ML of solution so that. . .

DETD As noted above, formulations of the present invention suitable for **oral** administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the. . . powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid **emulsion** or a water-in-oil liquid **emulsion**. The active ingredient may also be administered as a bolus, electuary or paste.

DETD Capsules comprising adenosine kinase inhibitors suitable for **oral** administration according to the methods of the present invention may be prepared as follows: (1) for a 10,000 capsule preparation:. . .

L31 ANSWER 15 OF 33 USPATFULL

AB The present invention is directed to certain novel compounds represented by structural formula I: ##STR1## or a pharmaceutically acceptable salt thereof, wherein R.sup.3, R.sup.6, R.sup.7, R.sup.8, R.sup.11, R.sup.12, R.sup.13, A, Q, W, X, Y, Z and n are defined herein. The invention is also concerned with pharmaceutical formulations comprising these novel compounds as active ingredients and the use of the novel compounds and their formulations in the treatment of certain disorders. The compounds of this invention are tachykinin receptor antagonists and are useful in the treatment of inflammatory diseases, pain or migraine, asthma and emesis.

AN 1998:51625 USPATFULL

TI Cycloalkyl tachykinin receptor antagonists

IN Caldwell, Charles G., Scotch Plains, NJ, United States
Chen, Ping, Old Bridge, NJ, United States
Durette, Philippe L., New Providence, NJ, United States
Finke, Paul, Milltown, NJ, United States
Hale, Jeffrey, Westfield, NJ, United States

Holson, Edward, New York, NY, United States
Kopka, Ihor, Millburn, NJ, United States
MacCoss, Malcolm, Freehold, NJ, United States
Meurer, Laura, Scotch Plains, NJ, United States
Mills, Sander G., Woodbridge, NJ, United States
Robichaud, Albert, Stirling, NJ, United States

PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

PI US 5750549 19980512 <--

AI US 1996-730277 19961015 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: McKane, Joseph

LREP Thies, J. Eric, Rose, David L.

CLMN Number of Claims: 30

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 8611

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5750549 19980512 <--

SUMM Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, **Alzheimer**'s disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases. . . al., Eur. J. Pharmacol., 249, R3-R4 (1993), F. D. Tattersall, et al., Neuropharmacology, 33, 259-260 (1994)], vasodilation, bronchospasm, reflex or **neuronal** control of the viscera [Mantyh et al., PNAS, 85, 3235-9 (1988)] and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes [Yankner et al., Science, 250, 279-82 (1990)] in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic. . .

SUMM . . . may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as **dementia**, including senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and. . . disorders, and diseases of the GI tract, such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, nausea, and emesis, including acute, delayed, post-operative, late-phase,. . .

SUMM . . . or treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, broncho-pneumonia,. . . as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain. . .

SUMM . . . conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for **oral** administration, suppositories for rectal administration,

sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

SUMM . . . ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, **emulsions**, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia,. . .

SUMM . . . may be incorporated for administration orally or by injection include aqueous solution, suitably flavoured syrups, aqueous or oil suspensions, and **emulsions** with acceptable oils such as cottonseed oil, sesame oil, **coconut oil** or peanut oil, or with a solubilizing or emulsifying agent suitable for **intravenous** use, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and. . .

SUMM . . . or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by. . .

SUMM . . . unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, **intravenous**, intramuscular, intrasternal injection or infusion techniques.

L31 ANSWER 16 OF 33 USPATFULL

AB The present invention relates to compounds of formula (I): wherein X is N or CH; and pharmaceutically acceptable salts and prodrugs thereof. The
compounds are of p articular use in the treatment of pain, inflammation,
migraine and emesis. ##STR1##

AN 1998:48409 USPATFULL

TI Morpholine derivatives and their use as antagonists of tachikinins

IN Haworth, Karen Elizabeth, Bishops Stortford, United Kingdom
Seward, Eileen Mary, Bishops Stortford, United Kingdom
Swain, Christopher John, Duxford, United Kingdom
Teall, Martin Richard, Bishops Stortford, United Kingdom

PA Merck Sharp & Dohme Ltd., Hoddesdon, England (non-U.S. corporation)

PI US 5747491 19980505 <--
WO 9530674 19951116 <--

AI US 1996-737035 19961101 (8)
WO 1995-GB983 19950501
19961101 PCT 371 date
19961101 PCT 102(e) date

PRAI GB 1994-8960 19940505
GB 1994-8963 19940505

DT Utility

FS Granted

EXNAM Primary Examiner: Ramsuer, Robert W.

LREP Thies, J. Eric, Rose, David L.

CLMN Number of Claims: 7

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1112

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5747491 19980505 <--
WO 9530674 19951116 <--

SUMM Evidence for the usefulness of tachykinin receptor antagonists in pain,

headache, especially migraine, **Alzheimer**'s disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases. . .

SUMM . . . [Lotz et al, Science (1988) 241, 1218-21 and Kimball et al, J. Immunol. (1988) 141(10), 3564-9] vasodilation, bronchospasm, reflex or **neuronal** control of the viscera [Mantyh et al, Proc. Natl. Acad. Sci., USA (1988) 85, 3235-9] and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes [Yankner et al, Science (1990) 250, 279-82] in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's Syndrome.

SUMM . . . tachykinin antagonists and which, by virtue of their advantageous aqueous solubility, are particularly easily formulated for administration by both the **oral** and injection routes, for example, in aqueous media.

SUMM While all of the usual routes of administration are useful with the above prodrugs, the preferred routes of administration are **oral** and **intravenous**. After gastrointestinal absorption or **intravenous** administration, the prodrugs are hydrolyzed or otherwise cleaved in vivo to the corresponding parent compound of formula (I), or a. . .

SUMM . . . the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for **oral**, parenteral or rectal administration, or administration by inhalation or insufflation.

SUMM . . . be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured **emulsions** with edible oils such as cottonseed oil, sesame oil, **coconut oil** or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include. . .

SUMM . . . the active ingredient, in association with a surface-active agent (or wetting agent or surfactant) or in the form of an **emulsion** (as a water-in-oil or oil-in-water **emulsion**).

SUMM Suitable **emulsions** may be prepared using commercially available fat **emulsions**, such as Intralipid.TM., Liposyn.TM., Infonutrol.TM., Lipofundin.TM. and Lipiphysan.TM.. The active ingredient may be either dissolved in a pre-mixed **emulsion** composition or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an **emulsion** formed upon mixing with a phospholipid (e.g. egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example gylcerol or glucose, to adjust the tonicity of the **emulsion**. Suitable **emulsions** will typically contain up to 20% oil, for example, between 5 and 20%. The fat **emulsion** will preferably comprise fat droplets between 0.1 and 1.0 .mu.m, particularly 0.1 and 0.5 .mu.m, and have a pH in. . .

SUMM Particularly preferred **emulsion** compositions are those prepared by mixing a compound of formula (I) with Intralipid.TM. or the components thereof (soybean oil, egg. . .

SUMM . . . or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically

acceptable solvents may be nebulised by. . .

SUMM . . . may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as **dementia**, including AIDS related **dementia**, senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and. . . neuropathological disorders such as peripheral neuropathy, for example AIDS related neuropathy, diabetic and chemotherapy-induced neuropathy, and postherpetic and other neuralgias; **neuronal** damage, such as cerebralischemic damage and cerebral edema in cerebrovascular disorders; small cell carcinomas such as small cell lung cancer;. . . such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera, ulcerative colitis, Crohn's disease, irritable bowel syndrome and emesis, including acute, delayed, post-operative, late phase or anticipatory. . .

DETD (**Emulsion**) Injection Formulation

DETD . . . The compound of formula (I) is dissolved directly in the commercially available Intralipid .TM. (10 or 20%) to form an **emulsion**.

DETD Alternative (**Emulsion**) Injectable Formulation

DETD All materials are sterilized and pyrogen free. The compound of formula (I) is dissolved in soybean oil. An **emulsion** is then formed by mining this solution with the egg phospholipid, glycerol and water. The **emulsion** is then sealed in sterile vials.

L31 ANSWER 17 OF 33 USPATFULL

AB A method for the treatment of cerebrovascular disorders and/or disorders associated with cerebral senility and/or other disorders which method comprises the administration of an effective, non-toxic amount of a compound of formula (I): ##STR1## or if appropriate a pharmaceutically acceptable salt thereof, wherein R.sup.1 and R.sup.2 each independently represent alkyl or a moiety of formula (a):

--(CH.sub.2).sub.m --A (a)

wherein

m represents zero or an integer 1, 2 or 3;

A represents a substituted or unsubstituted cyclic hydrocarbon radical; and

R.sup.3 represents a halogen atom, a nitro group, or a group --NR.sup.4 R.sup.5 wherein R.sup.4 and R.sup.5 each independently represents hydrogen, alkyl or alkylcarbonyl or R.sup.4 and R.sup.5 together with the nitrogen to which they are attached forming an optionally substituted, heterocyclic group; certain novel compounds falling within formula (I) and compositions comprising such compounds.

AN 1998:34066 USPATFULL

TI 8-substituted xanthine derivatives and method of use thereof

IN Spicer, Barbara Ann, Epsom, England
Smith, Harry, Epsom, England
Maschler, Harald, Nordstemmen, Germany, Federal Republic of

PA Beecham Group, Brentford, United Kingdom (non-U.S. corporation)

PI US 5734051 19980331 <--

AI US 1995-477157 19950607 (8)

RLI Division of Ser. No. US 1995-379092, filed on 26 Jan 1995, now abandoned
which is a continuation of Ser. No. US 1993-28765, filed on 9 Mar 1993, now abandoned which is a continuation of Ser. No. US 1990-497992, filed on 23 Mar 1990, now abandoned
PRAI GB 1989-6792 19890323
DT Utility
FS Granted
EXNAM Primary Examiner: Berh, Mark L.
LREP Dinner, Dara L., Venetianer, Stephen, Lentz, Edward T.
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1082
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5734051 19980331 <--
SUMM . . . improve data acquisition or retrieval following transient forebrain ischaemia and are therefore useful in the treatment of cerebral vascular and **neuronal** degenerative disorders associated with learning, memory and cognitive dysfunctions including cerebral senility, multi-infarct **dementia**, senile **dementia** of the **Alzheimer** type, age associated memory impairment and certain disorders associated with Parkinson's disease.
SUMM These compounds are also indicated to have neuroprotectant activity. They are therefore useful in the prophylaxis of disorders associated with **neuronal** degeneration resulting from ischaemic events, including cerebral ischaemia due to cardiac arrest, stroke and also after cerebral ischaemic events such. . .
SUMM . . . a method for the treatment of cerebrovascular disorders and/or disorders associated with cerebral senility and/or prophylaxis of disorders associated with **neuronal** degeneration resulting from ischaemic events and/or peripheral vascular disease and/or proliferative skin disease and/or for disorders of the respiratory tract. . .
SUMM . . . a medicament for the treatment of cerebrovascular disorders and/or disorders associated with cerebral senility and/or prophylaxis of disorders associated with **neuronal** degeneration resulting from ischaemic events and/or peripheral vascular disease and/or proliferative skin diseases and/or disorders of the respiratory tract and/or. . .
SUMM . . . for use in the treatment of cerebrovascular disorders and/or disorders associated with cerebral senility and/or prophylaxis of disorders associated with **neuronal** degeneration resulting from ischaemic events and/or peripheral vascular disease and/or proliferative skin diseases and/or disorders of the respiratory tract and/or. . .
SUMM . . . a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for **oral**, rectal, topical, parenteral, **intravenous** or intramuscular administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.
SUMM . . . be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as **oral** or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.
SUMM Unit dose presentation forms for **oral** administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin,. . .

SUMM The solid **oral** compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used. . .

SUMM **Oral** liquid preparations may be in the form of, for example, **emulsions**, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before. . . agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated **coconut oil**, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or. . .

L31 ANSWER 18 OF 33 USPATFULL

AB This invention provides compounds having the structure ##STR1## wherein m=0-1; and

n=0-1 or a pharmaceutically acceptable salt thereof when m and n=0, that are useful as neuroprotective agents.

AN 1998:17316 USPATFULL

TI 5H,8H-2-oxa-1,3,5,8-tetraaza-cyclopenta[b]-naphthalene-6,7-diones

IN Baudy, Reinhardt B., Yardley, PA, United States
Sulkowski, Theodore S., Wayne, PA, United States

PA American Home Products Corporation, Madison, NJ, United States (U.S. corporation)

PI US 5719153 19980217 <--

AI US 1996-692557 19960806 (8)

PRAI US 1995-2356 19950815 (60)

DT Utility

FS Granted

EXNAM Primary Examiner: Bernhardt, Emily

LREP Milowsky, Arnold S.

CLMN Number of Claims: 4

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 230

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5719153 19980217 <--

SUMM . . . has been suggested that accumulation of extracellular excitatory and neurotoxic amino acids, followed by hyperstimulation of neurons, may explain the **neuronal** degeneration seen in neurological diseases as Parkinsonism, senile **dementia**, Huntingtons chorea, and deficiencies of mental and motoric performance seen after conditions of brain ischaemia, anoxia and hypoglycemia. (E. G.. . .

SUMM . . . acute neurodegenerative disorders such as cerebral ischemia, convulsions, traumatic brain injury, and epilepsy. Specific applications also include therapy of senile **dementia Alzheimer** -type, parkinsonian **dementia** complex and other dominant or recessive spinocerebellar degenerations where AMPA antagonists prevent or retard the progression of the disease.

SUMM Liquid carriers are used in preparing solutions, suspensions, **emulsions**, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such. . . preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for **oral** and parenteral administration

include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated **coconut oil** and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl. . .

SUMM . . . such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid **emulsions** of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the. . .

SUMM . . . size, age and response pattern of the patient. Based on the results obtained in the standard pharmacological test procedures, projected **oral** daily dosages of active compound would be 1-500 mg/kg and preferably between 1-100 mg/kg. Projected **intravenous** daily dosages would be 0.1-75 mg/kg and preferably between 0.1-25 mg/kg.

Treatment will generally be initiated with small dosages less. . . of

the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached; precise dosages for **oral**, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated.

L31 ANSWER 19 OF 33 USPATFULL

AB Substituted heterocycles of the general structural formula: ##STR1## are

tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma and emesis, and calcium channel blockers useful in the treatment of cardiovascular conditions such as angina, hypertension or ischemia.

AN 1998:17310 USPATFULL

TI Morpholine and thiomorpholine tachykinin receptor antagonists

IN Dorn, Conrad P., Plainfield, NJ, United States
Finke, Paul E., Milltown, NJ, United States
Hale, Jeffrey J., Westfield, NJ, United States
MacCoss, Malcolm, Freehold, NJ, United States
Mills, Sander G., Woodbridge, NJ, United States
Shah, Shrenik K., Metuchen, NJ, United States
Chambers, Mark Stuart, North Bushey, England
Harrison, Timothy, Great Dunmow, England
Ladduwahetty, Tamara, Buckhurst Hill, England
Williams, Brian John, Great Dunnow, England

PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

PI US 5719147 19980217 <--

AI US 1995-525259 19950908 (8)

RLI Continuation-in-part of Ser. No. US 1993-169889, filed on 17 Dec 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-61914,

filed on 19 May 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-971448, filed on 4 Nov 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-905976, filed on 29 Jun 1992, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Grumbling, Matthew V.

LREP Thies, J. Eric, Rose, David L.

CLMN Number of Claims: 27

ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 8352
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5719147 19980217 <--
SUMM Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, **Alzheimer**'s disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases. . . Eur. J. Pharmacol., 249, R3-R4 (1993), F. D. Tattersall, et al., Neuropharmacology, 33, 259-260 (1994)], vasodilation, bronchospasm, reflex or **neuronal** control of the viscera [Mantyh et al., PNAS, 85, 3235-9 (1988)] and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes [Yankner et al., Science, 250, 279-82 (1990)] in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic. . .

SUMM . . . may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as **dementia**, including senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and. . . disorders, and diseases of the GI tract, such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, nausea, and emesis, including acute, delayed, post-operative, late-phase,. . .

SUMM . . . or treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, broncho-pneumonia,. . . as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain. . .

SUMM . . . conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for **oral** administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

SUMM . . . active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, **emulsions**, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia,. . .

SUMM . . . may be incorporated for administration orally or by injection include aqueous solution, suitably flavoured syrups, aqueous or oil suspensions, and **emulsions** with acceptable oils such as cottonseed oil, sesame oil, **coconut oil** or peanut oil, or with a solubilizing or emulsifying agent suitable for **intravenous** use, as well as elixirs and similar pharmaceutical

vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and. . .

SUMM . . . or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by. . .

SUMM . . . unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, **intravenous**, intramuscular, intrasternal injection or infusion techniques.

L31 ANSWER 20 OF 33 USPATFULL

AB Substituted heterocycles of the general structural formula: ##STR1## are

tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma, emesis and nausea.

AN 1998:14789 USPATFULL

TI Treatment of migraine with morpholine tachykinin receptor antagonists

IN Dorn, Conrad P., Plainfield, NJ, United States
MacCoss, Malcolm, Freehold, NJ, United States
Hale, Jeffrey J., Westfield, NJ, United States
Mills, Sander G., Woodbridge, NJ, United States

PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

PI US 5716942 19980210 <--

AI US 1995-450198 19950525 (8)

RLI Division of Ser. No. US 1994-206771, filed on 4 Mar 1994, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Jarvis, William R. A.

LREP Thies, J. Eric, Rose, David L.

CLMN Number of Claims: 20

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 6755

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5716942 19980210 <--

SUMM Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, **Alzheimer**'s disease, multiple sclerosis, attenuation of morphine withdrawal, cardivascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases. . . (1988) 141 (10) 3564-9 and A. Perianin, et al., Biochem. Biophys. Res Commun. 161, 520 (1989)) vasodilation, bronchospasm, reflex or **neuronal** control of the viscera (Mantyh et al., PNAS (1988) 85 3235-9) and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes (Yankner et al., Science, (1990) 250, 279-82) in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic. . .

SUMM While all of the usual routes of administration are useful with the present compounds, the preferred routes of administration are **oral** and **intravenous**. After gastrointestinal absorption or **intravenous** administration, the present compounds are hydrolyzed or otherwise cleaved in vivo to the corresponding parent compounds of formula I, wherein. . .

SUMM . . . include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related **dementia**, senile

dementia of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and. . . such as systemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; emesis, including acute, delayed, post-operative, late-phase, and anticipatory emesis,. . .

SUMM . . . or treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, broncho-pneumonia,. . . as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain. . .

SUMM . . . conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for **oral** administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

SUMM . . . ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, **emulsions**, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia,. . .

SUMM . . . be incorporated for administration orally or by injection include aqueous solution, suitably flavoured syrups, aqueous or oil suspensions, and flavoured **emulsions** with edible oils such as cottonseed oil, sesame oil, **coconut oil** or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include. . .

SUMM . . . or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by. . .

SUMM . . . unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, **intravenous**, intramuscular, intrasternal injection or infusion techniques.

DETD . . . was partitioned between 40 mL of ethyl ether and 20 mL of water; mixing of the layers resulted in an **emulsion**. Centrifugation at 2800 rpm for 15 minutes broke the **emulsion**; the aqueous layer was separated and lyophilized to afford 188 mg (33%) of the compound tentatively identified as 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(4-monophosphoryl-5-oxo-1H,-1,2,4-triazolo)methyl)-morpholine, dipotassium.

. .

L31 ANSWER 21 OF 33 USPATFULL

AB Substituted heterocycles of the general structural formula: ##STR1## are

tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma, and emesis.
AN 97:109895 USPATFULL
TI Morpholine compounds are prodrugs useful as tachykinin receptor antagonists
IN Dorn, Conrad P., Plainfield, NJ, United States
Hale, Jeffrey J., Westfield, NJ, United States
Maccoss, Malcolm, Freehold, NJ, United States
Mills, Sander G., Woodbridge, NJ, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 5691336 19971125 <--
AI US 1995-525870 19950908 (8)
RLI Continuation-in-part of Ser. No. US 1994-206771, filed on 4 Mar 1994, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Higel, Floyd D.
LREP Thies, J. Eric, Rose, David L.
CLMN Number of Claims: 25
ECL Exemplary Claim: 1,24
DRWN No Drawings
LN.CNT 7292
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5691336 19971125 <--
SUMM Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, **Alzheimer**'s disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases. . . al., Eur. J. Pharmacol., 249, R3-R4 (1993), F. D. Tattersall, et al., Neuropharmacology, 33, 259-260 (1994)], vasodilation, bronchospasm, reflex or **neuronal** control of the viscera [Mantyh et al., PNAS, 85, 3235-9 (1988)] and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes [Yankner et al., Science, 250, 279-82 (1990)] in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic. . .
SUMM While all of the usual routes of administration are useful with the present compounds, the preferred routes of administration are **oral** and **intravenous**. After gastrointestinal absorption or **intravenous** administration, the present compounds are hydrolyzed or otherwise cleaved in vivo to the corresponding parent compounds of formula I, wherein. . .
SUMM . . . may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as **dementia**, including senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and. . . disorders, and diseases of the GI tract, such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, nausea, and emesis, including acute, delayed, post-operative, late-phase,. . .
SUMM . . . or treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile **dementia** of the **Alzheimer** type,

Alzheimer's disease and Down's syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, broncho-pneumonia,. . . as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain. . .

SUMM . . . conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for **oral** administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

SUMM . . . ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, **emulsions**, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia,. . .

SUMM . . . be incorporated for administration orally or by injection include aqueous solution, suitably flavoured syrups, aqueous or oil suspensions, and flavoured **emulsions** with edible oils such as cottonseed oil, sesame oil, **coconut oil** or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include. . .

SUMM . . . or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by. . .

SUMM . . . unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, **intravenous**, intramuscular, intrasternal injection or infusion techniques.

DETD . . . was partitioned between 40 mL of ethyl ether and 20 mL of water; mixing of the layers resulted in an **emulsion**. Centrifugation at 2800 rpm for 15 minutes broke the **emulsion**; the aqueous layer was separated and lyophilized to afford 188 mg (33%) of the compound tentatively identified as 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(4-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)-morpholine, dipotassium. . .

DETD . . . ether and air dried. The solid was partitioned between 150 mL of ethyl ether and 150 mL of water; an **emulsion** formed on mixing of the layers. The **emulsion** was transferred into 50 mL centrifuge tubes; centrifugation at 3000 rpm for 15 minutes caused separation of the layers. The. . .

L31 ANSWER 22 OF 33 USPATFULL

AB This invention provides a novel series of non-peptidyl compounds which are useful in the treatment or prevention of a physiological disorder associated with an excess of tachykinins. This invention also provides methods for the treatment of such physiological disorders as well as pharmaceutical formulations which employ these novel compounds.

AN 97:101785 USPATFULL

TI Non-peptide tachykinin receptor antagonists

IN Cho, Sung Y., Indianapolis, IN, United States
Crowell, Thomas A., Indianapolis, IN, United States
Gitter, Bruce D., Carmel, IN, United States

Hipskind, Philip A., New Palestine, IN, United States
Howbert, J. Jeffry, Bellevue, WA, United States
Krushinski, Jr., Joseph H., Indianapolis, IN, United States
Lobb, Karen L., Indianapolis, IN, United States
Muehl, Brian S., Indianapolis, IN, United States
Nixon, James A., Indianapolis, IN, United States
PA Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)
PI US 5684033 19971104 <--
AI US 1995-463874 19950605 (8)
RLI Division of Ser. No. US 1993-153847, filed on 17 Nov 1993, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Shah, Mukund J.; Assistant Examiner: Wong, King Lit
LREP Gaylo, Paul J., Boone, David E.
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2235
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5684033 19971104 <--
SUMM . . . disorders may include disorders of the central nervous system such as anxiety, depression, psychosis, and schizophrenia; neurodegenerative disorders such as **dementia**, including senile **dementia** of the **Alzheimer**'s type, **Alzheimer**'s disease, AIDS-associated **dementia**, and Down's syndrome; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as peripheral. . . and disorders related to immune enhancement or suppression such as systemic lupus erythematosis; gastrointestinal disorders or diseases associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and irritable bowel syndrome; disorders of bladder function such as bladder. . . in the treatment of disorders of the central nervous system such as anxiety, psychosis, and schizophrenia; neurodegenerative disorders such as **Alzheimer**'s disease and Down's syndrome; respiratory diseases such as bronchospasm and asthma; inflammatory diseases such as inflammatory bowel disease, osteoarthritis and. . . arthritis; adverse immunological disorders such as rejection of transplanted tissues; gastrointestinal disorders and diseases such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and irritable bowel syndrome; incontinence; disorders of blood flow caused by. . .
SUMM . . . miosis; tissue transplant rejection; plasma extravasation resulting from cytokine chemotherapy and the like; spinal cord trauma; stroke; cerebral stroke (ischemia); **Alzheimer**'s disease; Parkinson's disease; multiple sclerosis; amyotrophic lateral sclerosis; schizophrenia; anxiety; and depression.
SUMM . . . are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes
including **oral**, rectal, transdermal, subcutaneous, **intravenous**, intramuscular, and intranasal. These compounds are effective as both injectable and **oral** compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active. . .
SUMM . . . the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, **emulsions**, solutions, syrups, aerosols (as a

solid or in a liquid medium), ointments containing for example up to 10%
by weight. . .
SUMM . . . be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored **emulsions** with edible oils such as cottonseed oil, sesame oil, **coconut oil**, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.
SUMM . . . liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use.
. .
DETD An **intravenous** formulation may be prepared as follows:

L31 ANSWER 23 OF 33 USPATFULL
AB This invention provides a novel series of non-peptidyl compounds which are useful in the treatment or prevention of a physiological disorder associated with an excess of tachykinins. This invention also provides methods for the treatment of such physiological disorders as well as pharmaceutical formulations which employ these novel compounds.
AN 97:86607 USPATFULL
TI Non-peptide tachykinin receptor antagonists
IN Cho, Sung Y., Indianapolis, IN, United States
Crowell, Thomas A., Indianapolis, IN, United States
Gitter, Bruce D., Carmel, IN, United States
Hipskind, Philip A., New Palestine, IN, United States
Howbert, J. Jeffry, Bellevue, WA, United States
Krushinski, Jr., Joseph H., Indianapolis, IN, United States
Lobb, Karen L., Indianapolis, IN, United States
Muehl, Brian S., Indianapolis, IN, United States
Nixon, James A., Indianapolis, IN, United States
PA Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)
PI US 5670499 19970923 <--
AI US 1995-462415 19950605 (8)
RLI Division of Ser. No. US 1993-153847, filed on 17 Nov 1993, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Haley, Jacqueline
LREP Gaylo, Paul J., Boone, David E.
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 4533
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5670499 19970923 <--
DETD . . . disorders may include disorders of the central nervous system such as anxiety, depression, psychosis, and schizophrenia; neurodegenerative disorders such as **dementia**, including senile **dementia** of the **Alzheimer**'s type, **Alzheimer**'s disease, AIDS-associated **dementia**, and Down's syndrome; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as peripheral. . . and disorders related to immune enhancement or suppression such as systemic lupus erythematosis; gastrointestinal disorders or diseases associated with the **neuronal** control of

viscera such as ulcerative colitis, Crohn's disease and irritable bowel syndrome; disorders of bladder function such as bladder. . . in the treatment of disorders of the central nervous system such as anxiety, psychosis, and schizophrenia; neurodegenerative disorders such as **Alzheimer**'s disease and Down's syndrome; respiratory diseases such as bronchospasm and asthma; inflammatory diseases such as inflammatory bowel disease, osteoarthritis and. . . arthritis; adverse immunological disorders such as rejection of transplanted tissues; gastrointestinal disorders and diseases such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and irritable bowel syndrome; incontinence; disorders of blood flow caused by. . .

DETD . . . miosis; tissue transplant rejection; plasma extravasation resulting from cytokine chemotherapy and the like; spinal cord trauma; stroke; cerebral stroke (ischemia); **Alzheimer**'s disease; Parkinson's disease; multiple sclerosis; amyotrophic lateral sclerosis; schizophrenia; anxiety; and depression.

DETD . . . are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including **oral**, rectal, transdermal, subcutaneous, **intravenous**, intramuscular, and intranasal. These compounds are effective as both injectable and **oral** compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active. . .

DETD . . . the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, **emulsions**, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight. . .

DETD . . . be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored **emulsions** with edible oils such as cottonseed oil, sesame oil, **coconut oil**, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

DETD . . . liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use.

. .

DETD An **intravenous** formulation may be prepared as follows:

L31 ANSWER 24 OF 33 USPATFULL

AB This invention provides methods for treating or preventing a condition associated with an excess of neuropeptide Y which methods comprise administration of one or more substituted benzofurans, benzothiophenes or indoles.

AN 97:78461 USPATFULL

TI Heterocyclic neuropeptide Y receptor antagonists

IN Bruns, Jr., Robert F., Carmel, IN, United States
Gehlert, Donald R., Indianapolis, IN, United States
Howbert, J. Jeffry, Bellevue, WA, United States
Lunn, William H. W., Indianapolis, IN, United States

PA Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)

PI US 5663192 19970902 <--

AI US 1994-326413 19941020 (8)

DT Utility
FS Granted
EXNAM Primary Examiner: Criares, Theodore J.
LREP Gaylo, Paul J., Boone, David E.
CLMN Number of Claims: 23
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1527
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5663192 19970902 <--
SUMM . . . compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or **emulsions** .
DETD . . . two hours after the addition of the stannous chloride was completed, resulting in the formation of a thick, beige, chalky **emulsion**. The solid was removed by filtration, stored overnight in one liter of water and then basified with a 25% solution. . .
DETD . . . neuropeptide Y and peptide YY with equal affinity. C. Wahlestedt, et al., Regulatory Peptides, 13:307-318 (1986); C. Wahlestedt, et al., **NEURONAL** MESSENGERS IN VASCULAR FUNCTION, 231-241 (Nobin, et al., eds. 1987). Substitution of the amino acid at position 34 with a. . .
DETD . . . such as cerebral infarction, neurodegeneration, epilepsy, stroke, and conditions related to stroke, cerebral vasospasm and hemorrhage, depression, anxiety, schizophrenia, and **dementia**;
DETD . . . are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including **oral**, rectal, transdermal, subcutaneous, **intravenous**, intramuscular, and intranasal. These compounds are effective as both injectable and **oral** compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active. . .
DETD . . . the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, **emulsions**, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight. . .
DETD . . . be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored **emulsions** with edible oils such as cottonseed oil, sesame oil, **coconut oil**, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.
DETD . . . liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use.
. .
DETD An **intravenous** formulation may be prepared as follows:
CLM What is claimed is:
. . . claim 1 wherein the physiological disorder associated with an excess of neuropeptide Y is selected from the group consisting of **dementia**, **Alzheimer**'s disease, Down's Syndrome, multiple sclerosis, cerebral stroke, and amyotrophic lateral sclerosis.

L31 ANSWER 25 OF 33 USPATFULL

AB The present invention is related to a pharmaceutical formulation which is an oil-in-water **emulsion** for parenteral and **oral** use which comprises

(i) an **emulsion**-stabilizing surface active drug in high concentration;

(ii) optionally a pharmacologically inert oil;

(iii) optionally a surfactant;

(iv) water or a buffer; and

(v) an agent giving isotonicity to the final formulation;

the use of and a process for preparation of the formulation.

AN 97:75826 USPATFULL

TI Preparing pharmaceutical formulation in form of oil-in-water **emulsion**

IN Lundquist, Stefan, Stockholm, Sweden

PA Astra Aktiebolag, Sodertalje, Sweden (non-U.S. corporation)

PI US 5660837 19970826 <--

AI US 1995-460046 19950602 (8)

RLI Division of Ser. No. US 1995-379486, filed on 30 Jan 1995

PRAI SE 1993-3281 19931007

DT Utility

FS Granted

EXNAM Primary Examiner: Lovering, Richard D.

LREP White & Case

CLMN Number of Claims: 2

ECL Exemplary Claim: 1

DRWN 4 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 582

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Preparing pharmaceutical formulation in form of oil-in-water **emulsion**

PI US 5660837 19970826 <--

AB The present invention is related to a pharmaceutical formulation which is an oil-in-water **emulsion** for parenteral and **oral** use which comprises

AB (i) an **emulsion**-stabilizing surface active drug in high concentration;

SUMM This invention relates to a novel pharmaceutical formulation comprising an **emulsion**-stabilizing surface active drug which may be administered parenterally or orally; and to the use of and a process for preparing. . .

SUMM . . . the CMZ-edisilate at room temperature (the product must be stored at +4.degree.-8.degree. C.) and the substantial sorption of CMZ by **intravenous** infusion giving sets. This sorption to plastics results in a safety problem in the clinic, especially when treating disorders requiring very accurate dosing. Finally, the **oral** liquid dosage form, a 5 w/v % syrup of CMZ-edisilate, also has a number of disadvantages such as poor stability. . .

SUMM . . . object of the invention is to provide a novel, clinically and pharmaceutically acceptable and useful formulation which is an oil-in-water **emulsion** for parenteral and **oral** use which comprises

SUMM (i) an **emulsion**-stabilizing surface active drug in high concentration;

SUMM The present invention is preferably related to **emulsion**-stabilizing surface active drugs having an anti-convulsant or sedative-hypnotic effect or drugs for preventing and/or treating neurodegeneration caused by acute and chronic neuropsychiatric disorders characterised by progressive processes that sooner or later lead to **neuronal** cell death and dysfunction. Such disorders include stroke; cerebral ischaemia; dysfunctions resulting from brain and/or spinal trauma; hypoxia and anoxia, such as from drowning, and including perinatal and neonatal hypoxic asphyxial brain damage; multi-infarct **dementia**; AIDS **dementia**; neurodegenerative diseases such as **Alzheimer**'s disease, Parkinson's disease, Huntington's chorea, epilepsy, multiple sclerosis and amytrophic lateral sclerosis; brain dysfunction in connection with surgery involving extracorporeal. . . to neurotoxins or radiation. This utility is manifested, for example, by the ability of the claimed formulation to inhibit delayed **neuronal** death in the gerbil bilateral occlusion model of ischaemia.

SUMM Preferred **emulsion**-stabilizing surface active drugs are the CMZ-base which is an oil at room temperature, and/or some analogues thereof which are oils. . . besides having a pharmacological effect, as a stabilizing surfactant or co-surfactant at the large interface in an oil in water **emulsion** system or in another aspect of the invention, functioning as the actual oil phase in an **emulsion** system.

SUMM . . . to the above mentioned drugs but could also be used to include any other drug which displays suitable amphiphilic and **emulsion**-stabilizing properties.

SUMM A conventional pharmacologically inert oil is included as a component in the formulation when the **emulsion**-stabilizing drug is not itself used as the internal oil phase.

SUMM . . . surfactant is included as a component in the formulation when the drug functions as the internal oil phase of the **emulsion**.

SUMM By means of the present invention the undesirable properties of both the parenteral and the **oral** dosage form, mentioned in the background of the invention, can be avoided. Certain compounds, because of their chemical stucture, have. . . fundamental changes in the nature of the interface which are of considerable importance in different contexts. For example, in an **emulsion** the adsorption of a surfactant at the oil-water interface lowers the interfacial tension thereby aiding in the dispersal of the. . . allow storage for a long period of time (typically two years) of pharmaceutically interesting two-phase systems such as for example **emulsions**. The geometrical shape of the amphiphilic molecule and the presence of any substituents in said molecule can have an appreciable effect on its stabilizing properties. Surprisingly, it has been found that e.g. CMZ and said analogues display excellent **emulsion**-stabilizing properties which allow **emulsions** of these compounds to be stored for a long period of time. Due to the geometrical shape and the amphiphilic properties of the drug molecule it is adsorbed at the surface of the droplets in the **emulsion**, forming a rigid and tightly packed interfacial film thereby reducing the possibility of collisions leading to droplet coalescence and consequently. . .

SUMM . . . number of other drugs with hydrophobic portions comprising aromatic and/or heterocyclic ring systems or a steroid skeleton also display good **emulsion**-stabilizing properties.

SUMM Examples of the types of drugs, besides CMZ and its analogues, which

have been found beneficial to use as **emulsion**-stabilizing agents include: antidepressants, neuroleptics, immunosuppressants, immunomodulators, antibiotics, antiinflammatory agents, proton pump inhibitors, calcium channel blockers, such as felodipine, and beta. . .

SUMM . . . usually observed that mixtures of conventional surfactants form even more stable systems than do single surfactants, even with very dilute **emulsions**, it has in some cases been found beneficial to use **emulsion**-stabilizing surface active drugs as co-surfactants together with any conventional pharmaceutically acceptable non-ionic surfactants, such as the poloxamers F68, F127 or. . .

SUMM . . . used by a person skilled in the art it is possible to manufacture a stable two-phase system like e.g. an **emulsion** of any appropriate drug mentioned above, where the stabilizing effect is due to the surface active drug alone or the. . . any other appropriate drug which is in the liquid state, could also function as the actual oil phase in an **emulsion** system in that way making it possible to incorporate a high concentration of the drug. In the latter case said. . .

DRWD FIG. 1A shows the .sup.13 C-NMR spectra of an **emulsion** with CMZ;

DRWD FIG. 1B shows the .sup.13 C-NMR spectra of an **emulsion** without CMZ;

DRWD . . . 2 shows changes in the chemical shifts of the carbonyl carbons of a phospholipid, located at the interface in the **emulsion** system, in the presence of CMZ; and

DETD . . . formulation in the former case can be established by known techniques such as .sup.13 C-NMR and a spectra of an **emulsion** with and without CMZ is shown in FIG. 1. Using .sup.13 C-NMR chemical shift determinations, it is possible to obtain information on the location of the CMZ-molecule in the **emulsion** system. For example, according to FIG. 2 the chemical shifts of the carbonyl carbons of a phospholipid, which are located at the interface in the **emulsion** system, is changed in the presence of CMZ. In fact, there is a linear relationship between the concentration of CMZ. . . of the carbonyl carbons (FIG. 2). The chemical shifts of the methylene carbons, being located in the core of the **emulsion** droplets is essentially unaffected by the presence of CMZ which can also be seen in FIG. 2. Notably, the effects. . . its immediate environment (.ltoreq.5 .ANG.), these findings clearly show that CMZ is primarily located in the surface region of the **emulsion** droplets.

DETD Surprisingly, it has been found that the presence of **emulsion** -stabilizing surface active drugs at the interface of an **emulsion** not only produces **emulsions** with excellent physical stability but also makes it possible to improve poor chemical stability of the drug in some cases,. . . any other appropriate drug which is in the liquid state has been used as the actual oil phase of an **emulsion**, thus allowing for a prolonged storage at room temperature. It has also become possible to substantially increase the drug concentration. . . Hence, the safety of e.g. CMZ in the clinic was improved by a substantially reduced sorption of the drug by **intravenous** infusion giving sets and moreover by giving the **emulsion** orally it was found that this type of formulation was also capable of improving the conventional liquid **oral** dosage form by a considerably better masking of the bitter taste of CMZ and at the same time solving the. . .

DETD in the case where the **emulsion**-stabilizing surface active drug is not itself used as the internal oil phase by

DETD adding the **emulsion**-stabilizing surface active drug and an optional conventional surfactant to a two-phase, oil-water-system at room temperature;

DETD allowing the **emulsion**-stabilizing surface active drug or the **emulsion**-stabilizing surface active drug together with the conventional surfactant to equilibrate at the interface;

DETD homogenizing by high pressure technique whereby a stable **emulsion** is obtained which has a droplet size distribution where the main fraction is below 200 nm;

DETD dispersing the **emulsion**-stabilizing surface active drug together with a conventional surfactant in water at room temperature;

DETD homogenizing by high pressure technique; whereby a stable **emulsion** is obtained which has a droplet size distribution where the main fraction is below 200 nm.

DETD This novel formulation comprises in general the **emulsion**-stabilizing surface active drug in a concentration from about 0.01 to 5% w/v.

DETD More particularly, the novel formulation of the invention comprises: a) the **emulsion**-stabilizing surface active drug in an amount of from about 0.01 to 5.0 g per 100 ml of the final formulation;. . . such as soybean oil, safflower oil, sesame oil, peanut oil, cottonseed oil, borago oil, sunflower oil, corn oil, olive oil, **medium chain triglycerides** (such as Miglyol.RTM.), or acetylated monoglycerides; c) a surfactant in an amount of from about 0.1 to 20 g per. . .

DETD The administration in the novel method of treatment of this invention may conveniently be **oral** or parenteral at a dosage level of, for example, about 1 to 3000 mg/kg, preferably about 10 to 1000 mg/kg. . . . 1 to 4 doses or treatments per day. The dose will depend on the route of administration preferred routes being **oral** or **intravenous** administration. It will be appreciated that the severity of the disease, the age of the patient and other factors normally. . .

DETD Oil-in-water **emulsions** of CMZ for **intravenous** and **oral** use were prepared from the following components:

DETD In a first step the **emulsion**-stabilizing drug and a surfactant were added to a two-phase system, oil-water, at room temperature and were subsequently allowed to equilibrate at the interface. This formulation, together with additional indicated components in the formula, was homogenized and the resulting **emulsion** was stable and had an average droplet size below 100 nm and could easily be sterile filtered (200 nm filter).

DETD Oil-in-water **emulsions** were prepared as described in Examples 1-2 with the following components:

DETD Oil-in-water **emulsions** were prepared as described in Examples 1-2 with the following components:

DETD Oil-in-water **emulsions**, according to Examples 9-12, were prepared with the only difference that a sodium carbonate buffer pH 7.0 was used to. . .

DETD Oil-in-water **emulsions** were prepared as described in Examples 1-2 with the following components:

DETD Oil-in-water **emulsions** were prepared according to Examples 17-20 with the only difference that a sodium carbonate buffer pH 7.0 was used to. . .

DETD Oil in water **emulsions**, where the **emulsion**-stabilizing drug was used as the sole stabilizing agent in the system,

were prepared from the following components:

DETD In a first step the **emulsion**-stabilizing drug was added to a two-phase system, oil-water, at room temperature and was subsequently allowed to equilibrate at the interface. This formulation, together with additional indicated components in the formula, was homogenized and the resulting **emulsion** was stable and had an average droplet size below 100 nm and could easily be sterile filtered (200 nm filter).

DETD Oil in water **emulsions** were prepared as described in Examples 25-26 with the following components:

DETD **Emulsions** where the drug functions as the internal oil-phase of the system were prepared from the following components:

DETD In a first step the drug was dispersed in water at room temperature. An **emulsion** was then prepared from the resulting drug-water dispersion, together with additional indicated components in the formula. The resulting **emulsion** was stable and had an average droplet size below 100 nm and could easily be sterile filtered (200 nm filter).

DETD **Emulsions** according to Examples 31-32 were prepared with the following components:

DETD **Emulsions** according to Examples 31-32 were prepared with the following components:

DETD **Emulsions** according to Examples 39-42 were prepared with the only difference that a sodium carbonate buffer pH 7.0 was used to. . .

CLM What is claimed is:

1. A process for the preparation of a pharmaceutical formulation in the form of an oil-in-water **emulsion** comprising the steps of: (a) in the case where an **emulsion**-stabilizing surface active drug is not itself used as the internal oil phase, (i) adding the **emulsion**-stabilizing surface active drug and an optimal conventional surfactant to a two-phase, oil-water system at room temperature; (ii) allowing the **emulsion**-stabilizing surface active drug or the **emulsion**-stabilizing surface active drug together with the conventional surfactant to equilibrate at an interface of oil and water; (iii) adding an agent giving isotonicity to the final formulation; and (iv) homogenizing by high pressure technique; whereby a stable **emulsion** is-obtained which has a droplet size distribution where the main fraction is below 200 nm; or (b) in the case where the drug functions as the internal oil phase of the system, (i) dispersing the **emulsion**-stabilizing surface active drug together with a conventional surfactant in water at room temperature; (ii) allowing the surfactant to equilibrate at. . . (iii) adding an agent giving isotonicity to the final formulation; and (iv) homogenizing by high pressure technique; whereby a stable **emulsion** is obtained which has a droplet size distribution where the main fraction is below 200 nm.

L31 ANSWER 26 OF 33 USPATFULL

AB Substituted heterocycles of the general structural formula: ##STR1## are tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma and emesis, and calcium channel blockers useful in the treatment of cardiovascular conditions such as angina, hypertension or ischemia.

AN 97:49744 USPATFULL
TI Process for preparing morpholine tachykinin receptor antagonists
IN Dorn, Conrad P., Plainfield, NJ, United States
Hale, Jeffrey J., Westfield, NJ, United States
Finke, Paul E., Milltown, NJ, United States
MacCoss, Malcolm, Freehold, NJ, United States
Mills, Sander G., Woodbridge, NJ, United States
Shah, Shrenik K., Metuchen, NJ, United States
Chambers, Mark S., Watford Harts, England
Harrison, Timothy, Great Dunmow, England
Ladduwahetty, Tamara, Buckhurst Hill, England
Williams, Brian J., Great Dunnow, England
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 5637699 19970610 <--
AI US 1995-445489 19950522 (8)
RLI Division of Ser. No. US 1993-169889, filed on 17 Dec 1993, now abandoned
which is a continuation-in-part of Ser. No. US 1993-61914, filed on 19 May 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-971448, filed on 4 Nov 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-905976, filed on 29 Jun 1992, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Grumbling, Matthew V.
LREP Thies, J. Eric, Rose, David L.
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 6269
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5637699 19970610 <--
SUMM Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, **Alzheimer**'s disease, multiple sclerosis, attenuation of morphine withdrawal, cardivascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases. . . al., J. Immunol. (1988)141 (10) 3564-9 and A. Perianin,
et al., Biochem. Biophys. Res Commun. 161,520 (1989))vasodilation, bronchospasm, reflex or **neuronal** control of the viscera (Mantyh et al., PNAS (1988) 85 3235-9) and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes (Yankner et al., Science, (1990) 250, 279-82) in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic. . .
DETD . . . include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as ADS related **dementia**, senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and. . . such as systemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; emesis, including acute, delayed, post-operative, late-phase, and anticipatory emesis,. . .
DETD . . . or treatment of disorders of the central nervous system such as

anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, broncho-pneumonia,. . . as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain. . .

DETD . . . conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for **oral** administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

DETD . . . ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, **emulsions**, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia,. . .

DETD . . . be incorporated for administration orally or by injection include aqueous solution, suitably flavored syrups, aqueous or oil suspensions, and flavored **emulsions** with edible oils such as cottonseed oil, sesame oil, **coconut oil** or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include. . .

DETD . . . or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by. . .

DETD . . . unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, **intravenous**, intramuscular, intrastemal injection or infusion techniques.

L31 ANSWER 27 OF 33 USPATFULL

AB The present invention relates to compounds of formula (I), wherein R.sup.1 is hydrogen, halogen, C.sub.1-6 C alkyl, C.sub.1-6 alkoxy, CF.sub.3, NO.sub.2, CN, SR.sup.a, SOR.sup.a, SO.sub.2 R.sup.a, CO.sub.2 R.sup.a, CONR.sup.a R.sup.b, C.sub.2-6 alkenyl, C.sub.2-6 alkynyl or C.sub.1-4 alkyl substituted by C.sub.1-4 alkoxy, where R.sup.a and R.sup.b are hydrogen or C.sub.1-4 alkyl; R.sup.2 is hydrogen, halogen, C .sub.1-6 alkyl, C.sub.1-6 alkoxy substituted by C.sub.1-4 alkoxy or CF.sub.3 ; R.sup.3 is hydrogen, halogen or CF.sub.3 ; R.sup.4 is selected from the definitions of R.sup.1 ; R.sup.5 is selected from the definitions of R.sup.2 ; R.sup.6 is a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by .dbd.O, .dbd.S or a C.sub.1-4 alkyl group, and optionally substituted by an aminoalkyl group; R.sup.9a and R.sup.9b are hydrogen or C.sub.1-4 alkyl, or R.sup.9a and R.sup.9b are joined to form a C.sub.5-7 ring; X is C.sub.1-4 alkylene optionally substituted by oxo; and Y is a C.sub.1-4 alkyl group optionally substituted by hydroxyl; with the proviso that if Y is C.sub.1-4 alkyl, R.sup.6 is substituted at least by an aminoalkyl group; and pharmaceutically acceptable salts and

prodrugs thereof. The compounds are of particular use in the treatment of pain, inflammation, migraine and emesis.

AN 97:22780 USPATFULL

TI Substituted morpholine derivatives and their use as therapeutic agents

IN Baker, Raymond, Green Tye, United Kingdom
Harrison, Timothy, Great Dunmow, United Kingdom
MacLeod, Angus M., Bishops Stortford, United Kingdom
Owens, Andrew P., Rushden, United Kingdom
Seward, Eileen M., Bishops Stortford, United Kingdom
Swain, Christopher J., Duxford, United Kingdom
Teall, Martin R., Bishops Stortford, United Kingdom

PA Merck Sharp & Dohme Limited, Hoddesdon, England (non-U.S. corporation)

PI US 5612337 19970318 <--
WO 9518124 19950706 ##STR1## <--

AI US 1996-663201 19960613 (8)
WO 1994-GB2819 19941223
19960613 PCT 371 date
19960613 PCT 102(e) date

PRAI GB 1993-26480 19931229
GB 1994-7189 19940412
GB 1994-8065 19940422
GB 1994-16428 19940815

DT Utility

FS Granted

EXNAM Primary Examiner: Ramsuer, Robert W.

LREP Thies, J. Eric, Rose, David L.

CLMN Number of Claims: 24

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 3715

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5612337 19970318 <--
WO 9518124 19950706 ##STR1## <--

SUMM Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, **Alzheimer**'s disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases. . .

SUMM . . . [Lotz et al, Science (1988) 241, 1218-21 and Kimball et al, J. Immunol. (1988) 141(10), 3564-9] vasodilation, bronchospasm, reflex or **neuronal** control of the viscera [Mantyh et al, PNAS (1988) 85, 3235-9] and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes [Yankner et al, Science (1990) 250, 279-82] in
senile **dementia** of the **Alzheimer** type,
Alzheimer's disease and Down's Syndrome.

SUMM . . . tachykinin antagonists and which, by virtue of their advantageous aqueous solubility, are particularly easily formulated for administration by both the **oral** and injection routes, for example in aqueous media.

SUMM While all of the usual routes of administration are useful with the above prodrugs, the preferred routes of administration are **oral** and **intravenous**. After gastrointestinal absorption or **intravenous** administration, the prodrugs are hydrolyzed or otherwise cleaved in vivo to the corresponding parent compounds of formula (I), or a. . .

SUMM . . . the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories,
for **oral**, parenteral or rectal administration, or

administration by inhalation or insufflation.

SUMM . . . be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured **emulsions** with edible oils such as cottonseed oil, sesame oil, **coconut oil** or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include. . .

SUMM . . . the active ingredient, in association with a surface-active agent (or wetting agent or surfactant) or in the form of an **emulsion** (as a water-in-oil or oil-in-water **emulsion**).

SUMM Suitable **emulsions** may be prepared using commercially available fat **emulsions**, such as Intralipid.TM., Liposyn.TM., Infonutrol.TM., Lipofundin.TM. and Lipiphysan.TM.. The active ingredient may be either dissolved in a pre-mixed **emulsion** composition or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an **emulsion** formed upon mixing with a phospholipid (e.g. egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example gylcerol or glucose, to adjust the tonicity of the **emulsion**. Suitable **emulsions** will typically contain up to 20% oil, for example, between 5 and 20%. The fat **emulsion** will preferably comprise fat droplets between 0.1 and 1.0 .mu.m, particularly 0.1 and 0.51 .mu.m, and have a pH in. . .

SUMM Particularly preferred **emulsion** compositions are those prepared by mixing a compound of formula (I) with Intralipid.TM. or the components thereof (soybean oil, egg. . .

SUMM . . . or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by. . .

SUMM . . . may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as **dementia**, including senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, for. . . such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera, ulcerative coliris, Crohn's disease, irritable bowel syndrome and emesis, including acute, delayed or anticipatory emesis such as. . .

DETD EXAMPLE 106B--(**Emulsion**) Injection Formulation

DETD The compound of formula (I) is dissolved directly in the commercially available Intralipid.TM. (10 or 20%) to form an **emulsion**.

DETD EXAMPLE 106C--Alternative (**Emulsion**) Injectable Formulation

DETD All materials are sterilized and pyrogen free. The compound of formula (I) is dissolved in soybean oil. An **emulsion** is then formed by mixing this solution with the egg phospholipid, glycerol and water. The **emulsion** is then sealed in sterile vials.

L31 ANSWER 28 OF 33 USPATFULL

AB N-Acylpiperidines of general structure ##STR1## are tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma and emesis.

AN 97:20534 USPATFULL
TI N-acylpiperidine tachykinin antagonists
IN MacCoss, Malcolm, Freehold, NJ, United States
Mills, Sander G., Woodbridge, NJ, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 5610165 19970311 <--
AI US 1994-198025 19940217 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Owens, Amelia A.
LREP Thies, J. Eric, Rose, David L.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2279
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5610165 19970311 <--
SUMM Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, **Alzheimer**'s disease, multiple sclerosis, attenuation of morphine withdrawal, cardivascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases. . . (1988) 141 (10) 3564-9 and A. Perianin, et al., Biochem, Biophys. Res Commun. 161, 520 (1989)) vasodilation, bronchospasm, reflex or **neuronal** control of the viscera (Mantyh et al., PNAS (1988) 85 3235-9) and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes (Yankner et al., Science, (1990) 250, 279-82) in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic. . .
SUMM . . . include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related **dementia**, senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and. . . such as systemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; emesis, including acute, delayed, post-operative, late-phase, and anticipatory emesis,. . .
SUMM . . . or treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, broncho-pneumonia,. . . as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain. . .
SUMM . . . conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for **oral** administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.
SUMM . . . active ingredient may be compounded, for example, with the

usual non-toxic, pharmaceutically acceptable carders for tablets, pellets, capsules, suppositories, solutions, **emulsions**, suspensions, and any other form suitable for use. The carders which can be used are water, glucose, lactose, gum acacia,. . .

SUMM . . . be incorporated for administration orally or by injection include aqueous solution, suitably flavoured syrups, aqueous or oil suspensions, and flavoured **emulsions** with edible oils such as cottonseed oil, sesame oil, **coconut oil** or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include. . .

SUMM . . . or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by. . .

SUMM . . . unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, **intravenous**, intramuscular, intrastemal injection or infusion techniques.

L31 ANSWER 29 OF 33 USPATFULL

AB Disclosed are substituted aryl piperazines of Formula I ##STR1## are tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma and emesis. In particular compounds of Formula I are shown to be neurokinin antagonists.

AN 97:18161 USPATFULL

TI Substituted aryl piperazines as neurokinin antagonists

IN Chiang, Yuan-Ching P., Scotch Plains, NJ, United States
Finke, Paul E., Milltown, NJ, United States
Maccoss, Malcolm, Freehold, NJ, United States
Meurer, Laura C., Scotch Plains, NJ, United States
Miller, Daniel J., Edison, NJ, United States
Mills, Sander G., Woodbridge, NJ, United States
Robichaud, Albert J., Stirling, NJ, United States
Shah, Shrenik K., Metuchen, NJ, United States

PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

PI US 5607936 19970304 <--

AI US 1994-316013 19940930 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Gerstl, Robert

LREP Panzer, Curtis C., Rose, David L.

CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 2690

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5607936 19970304 <--

SUMM . . . (1988) 141 (10) 3564-9 and A. Perianin, et al., Biochem. Biophys. Res. Commun. 161, 520 (1989)) vasodilation, bronchospasm, reflex or **neuronal** control of the viscera (Mantyh et al., PNAS (1988) 85 3235-9) and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes (Yankner et al., Science, (1990) 250, 279-82) in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic. . .

SUMM . . . include disorders of the central nervous system such as

anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related **dementia**, senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as. . . such as systemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, incontinence, nausea, and emesis, including acute, delayed, post-operative,. . .

SUMM . . . unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, **intravenous**, intramuscular, intracisternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle,. . .

SUMM The pharmaceutical compositions containing the active ingredient may be in a form suitable for **oral** use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, **emulsions**, hard or soft capsules, or syrups or elixirs. Compositions intended for **oral** use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such. . .

SUMM Formulations for **oral** use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent,. . .

SUMM . . . be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or **coconut oil**, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax,. . . cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable **oral** preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

SUMM The pharmaceutical compositions of the invention may also be in the form of oil-in-water **emulsions**. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for. . . example, sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The **emulsions** may also contain sweetening and flavoring agents.

L31 ANSWER 30 OF 33 USPATFULL

AB Substituted heterocycles of the structural formula: ##STR1## are tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma, emesis and nausea.

AN 96:36566 USPATFULL

TI Treatment of emesis with morpholine tachykinin receptor antagonists

IN Dorn, Conrad P., Plainfield, NJ, United States
MacCoss, Malcolm, Freehold, NJ, United States
Hale, Jeffrey J., Westfield, NJ, United States
Mills, Sander G., Woodbridge, NJ, United States

PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

PI US 5512570 19960430 <--

AI US 1995-450507 19950525 (8)

RLI Division of Ser. No. US 1994-206771, filed on 4 Mar 1994
DT Utility
FS Granted
EXNAM Primary Examiner: Higel, Floyd D.
LREP Thies, J. Eric, Rose, David L.
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 6501
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5512570 19960430 <--
SUMM Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, **Alzheimer**'s disease, multiple sclerosis, attenuation of morphine withdrawal, cardivascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases. . . (1988) 141 (10) 3564-9 and A. Perianin, et al., Biochem. Biophys. Res Commun. 161, 520 (1989)) vasodilation, bronchospasm, reflex or **neuronal** control of the viscera (Mantyh et al., PNAS (1988) 85 3235-9) and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes (Yankner et al., Science, (1990) 250, 279-82) in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic. . .
DETD While all of the usual routes of administration are useful with the present compounds, the preferred routes of administration are **oral** and **intravenous**. After gastrointestinal absorption or **intravenous** administration, the present compounds are hydrolyzed or otherwise cleaved in vivo to the corresponding parent compounds of formula I, wherein. . .
DETD . . . include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related **dementia**, senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and. . . such as systemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; emesis, including acute, delayed, post-operative, late-phase, and anticipatory emesis,. . .
DETD . . . or treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, broncho-pneumonia,. . . as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain. . .
DETD . . . conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for **oral** administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.
DETD . . . ingredient may be compounded, for example, with the usual non-

toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, **emulsions**, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia,. . .

DETD . . . be incorporated for administration orally or by injection include aqueous solution, suitably flavoured syrups, aqueous or oil suspensions, and flavoured **emulsions** with edible oils such as cottonseed oil, sesame oil, **coconut oil** or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include. . .

DETD . . . or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by. . .

DETD . . . unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, **intravenous**, intramuscular, intrasternal injection or infusion techniques.

DETD . . . was partitioned between 40 mL of ethyl ether and 20 mL of water; mixing of the layers resulted in an **emulsion**. Centrifugation at 2800 rpm for 15 minutes broke the **emulsion**; the aqueous layer was separated and lyophilized to afford 188 mg (33%) of the compound tentatively identified as 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(4-monophosphoryl-5-oxo-1H. . .

L31 ANSWER 31 OF 33 USPATFULL

AB Disclosed are spiro-substituted azacycles of formula I ##STR1## are selective neurokinin-3 antagonists useful in the treatment of CNS disorders.

AN 95:64928 USPATFULL

TI Spiro-substituted azacycles as neurokinin-3 antagonists

IN Shah, Shrenik K., Metuchen, NJ, United States

PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

PI US 5434158 19950718 <--

AI US 1994-233487 19940426 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Tsang, Cecilia

LREP Panzer, Curtis C., Rose, David L.

CLMN Number of Claims: 4

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1318

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5434158 19950718 <--

SUMM . . . Immunol. (1988) 141 (10) 3564-9 and A. Perianin, et al., Biochem. Biophys. Res. Commun. 161,520 (1989)) vasodilation, bronchospasm, reflex or **neuronal** control of the viscera (Mantyh et al., PNAS (1988) 85 3235-9) and, possibly by arresting or slowing .beta.-amyloid-mediated neurodegenerative changes (Yankner et al., Science, (1990) 250, 279-82) in senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic. . .

DETD . . . include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative

disorders such as AIDS related **dementia**, senile **dementia** of the **Alzheimer** type, **Alzheimer**'s disease and Down's syndrome; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as. . . such as systemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the **neuronal** control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of bladder function; fibrosing and collagen diseases such. . .

DETD . . . unit formulations containing conventional non-toxic pharmaceutically acceptable carders, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, **intravenous**, intramuscular, intracistemal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle,. . .

DETD The pharmaceutical compositions containing the active ingredient may be in a form suitable for **oral** use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, **emulsions**, hard or soft capsules, or syrups or elixirs. Compositions intended for **oral** use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such. . .

DETD Formulations for **oral** use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent,. . .

DETD . . . be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or **coconut oil**, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax,. . . cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable **oral** preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

DETD The pharmaceutical compositions of the invention may also be in the form of oil-in-water **emulsions**. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for. . . example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The **emulsions** may also contain sweetening and flavoring agents.

L31 ANSWER 32 OF 33 USPATFULL
AN 95:36408 USPATFULL
TI Xanthine derivatives
IN Smith, David G., SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epson, Surrey, England
Buckle, Derek R., SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epson, Surrey, England
Fenwick, Ashley E., SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epson, Surrey, England KT18 5XQ
PI US 5409934 19950425 <--
WO 9211260 19920709 <--
AI US 1993-78152 19930707 (8)
WO 1991-GB2286 19911219
19930707 PCT 371 date
19930707 PCT 102(e) date

PRAI GB 1990-27752 19901221
GB 1990-27899 19901221
DT Utility
FS Granted
EXNAM Primary Examiner: Berch, Mark L.
LREP Kanagy, James, Suter, Stuart, Lentz, Edward
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1348
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5409934 19950425 <--
WO 9211260 19920709 <--
SUMM . . . improve data aquisition or retrieval following transient forebrain ischaemia and are therefore useful in the treatment of cerebral vascular and **neuronal** degenerative disorders associated with learning, memory and cognitive dysfunctions including cerebral senility, multi-infarct **dementia**, senile **dementia** of the **Alzheimer** type, age associated memory impairment and certain disorders associated with Parkinson's disease.
SUMM These compounds are also indicated to have neuroprotectant activity. They are therefore useful in the prophylaxis of disorders associated with **neuronal** degeneration resulting from ischaemic events, including cerebral ischaemia due to cardiac arrest, stroke and also after cerebral ischaemic events such. . .
SUMM . . . salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatments mentioned hereinbefore, such as cerebral vascular and **neuronal** denerative disorders associated with learning, memory and cognitive dysfunctions, peripheral vascular disease or proliferate skin disease or for the prophylaxis of disorders associated with **neuronal** degeneration resulting from ischaemic events or for the inhibition of the production of tumour necrosis factor in for example the. . .
SUMM . . . a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for **oral**, rectal, topical, parenteral, **intravenous** or intramuscular administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.
SUMM . . . be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as **oral** or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.
SUMM Unit dose presentation forms for **oral** administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin,. . .
SUMM The solid **oral** compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used. . .
SUMM **Oral** liquid preparations may be in the form of, for example, **emulsions**, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before. . . agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated **coconut oil**, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or. . .

L31 ANSWER 33 OF 33 USPATFULL
AB A compound of formula (I) or a pharmaceutically acceptable salt thereof:

##STR1## wherein: R.sub.1 is --CH.sub.3 or --CH.sub.2 CH.sub.3 unsubstituted or substituted by 1 to 3 fluorines;

X is O or S(O).sub.s where s=0 to 2;

R.sub.2 is C.sub.4 -C.sub.6 cyclic alkyl, optionally substituted by one to three methyl groups or one ethyl group; --CH.sub.2 -cyclopentyl, --CH.sub.2 -cyclopropyl, 3-tetrahydrofuranyl, C.sub.1-7 alkyl, CH.sub.3 or CH.sub.2 CH.sub.3 substituted by one to three fluorines;

--(CH.sub.2).sub.n COO(CH.sub.2).sub.g CH.sub.3, or (CH.sub.2).sub.n O(CH.sub.2).sub.g CH.sub.3, wherein n is 2 to 4 and g is 0 to 2;

R.sub.3 represents a moiety of formula (a); ##STR2## wherein R.sub.4 and R.sub.5 each represent hydrogen or R.sub.4 and R.sub.5 together represent a bond;

B represents >C.dbd.O, >C.dbd.S or >CH--R.sub.6 wherein R.sub.6 represents H, OH, C.sub.1-6 alkoxy or C.sub.1-6 thioalkoxy; and m and r each independently represents zero or an integer in the range of 1 to 4 wherein m+r represents an integer in the range of from 2 to 4; with the proviso that when R.sub.1 is methyl, X is oxygen, R.sub.2 is methyl or cyclopenyl, R.sub.3 does not represent cyclopent-1,2-ene-3-one.

AN 94:97751 USPATFULL
TI Phenyl-substituted cycloalkenyl compounds useful as PDE IV inhibitors
IN Maschler, Harald, Nordstemmen, Germany, Federal Republic of
Christensen, IV, Siegfried B., King of Prussia, PA, United States
PA SmithKline Beecham Pharma GmbH, Munich, Germany, Federal Republic of (non-U.S. corporation)
SmithKline Beecham Corporation, King of Prussia, PA, United States (U.S. corporation)
PI US 5362915 19941108 <--
WO 9115451 19911017 <--
AI US 1992-934546 19921002 (7)
WO 1991-EP637 19910402
19921002 PCT 371 date
19921002 PCT 102(e) date
PRAI GB 1990-7762 19900405
DT Utility
FS Granted
EXNAM Primary Examiner: Richter, Johann; Assistant Examiner: Hydorn, Michael B.
LREP Kanagy, James M., Suter, Stuart R., Lentz, Edward T.
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1007
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5362915 19941108 <--
WO 9115451 19911017 <--
SUMM . . . improve data acquisition or retrieval following transient forebrain ischaemia and are therefore useful in the treatment of cerebral vascular and **neuronal** degenerative disorders associated with learning, memory and cognitive dysfunctions including cerebral senility, multi-infarct **dementia**, senile

dementia of the **Alzheimer** type, age associated memory impairment and certain disorders associated with Parkinson's disease.

SUMM These compounds are also indicated to have neuroprotectant activity. They are therefore useful in the prophylaxis of disorders associated with **neuronal** degeneration resulting from ischaemic events, including cerebral ischaemia due to cardiac arrest, stroke and also after cerebral ischaemic events such. . .

SUMM . . . a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for **oral**, rectal, topical, parenteral, **intravenous** or intramuscular administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.

SUMM . . . be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as **oral** or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.

SUMM Unit dose presentation forms for **oral** administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin,. . .

SUMM The solid **oral** compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used. . .

SUMM **Oral** liquid preparations may be in the form of, for example, **emulsions**, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before. . . agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated **coconut oil**, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or. . .

SUMM The invention further provides a method of treatment in mammals, including humans, of cerebrovascular disorders and/or **neuronal** degenerative disorders associated with learning, memory and cognitive dysfunctions, including cerebral senility, multi-infarct **dementia** and senile **dementia** of the **Alzheimer** type, which comprises administering to the sufferer an effective, non-toxic amount of a compound of formula (I).

SUMM In yet a further aspect, the present invention provides a method for the prophylaxis of disorders associated with **neuronal** degeneration, following an ischaemic event in mammals, especially humans, which method comprises the administration to the sufferer of an effective,. . .

SUMM . . . use of a compound of formula (I) for the manufacture of a medicament for the treatment of cerebral vascular and **neuronal** degenerative disorders associated with learning, memory and cognitive dysfunctions including cerebral senility, multi-infarct **dementia** and senile **dementia** of the **Alzheimer** type and/or disorders resulting from an ischaemic event and/or peripheral vascular disease and/or proliferative skin diseases and/or reversible airways obstruction. . .

SUMM Each dosage unit for **oral** administration contains suitably from 1 mg to 100 mg/Kg, and preferably from 10 mg to 30 mg, and each dosage. . .

SUMM The daily dosage regimen for **oral** administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound formula (I) or a pharmaceutically acceptable salt thereof. . . (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for intranasal administration and **oral** inhalation is suitably about 10 to about 1200 .mu.g/person. The acitve ingredient may be administered from 1 to 6 times. . .